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بسمه تعالی

معاونت غذا و دارو

مدیریت محترم درمان تامین اجتماعی استان اصفهان

مدیر محترم شبکه بهداشت و درمان شهرستان .....(کلیه شبکه ها)

روسای محترم مراکز آموزشی درمانی/ بیمارستان‌های دانشگاه علوم پزشکی اصفهان

روسای محترم بیمارستان‌های خصوصی، خیریه و وابسته با سازمان‌ها و نهادها

با سلام و احترام

به پیوست نامه شماره ۶۵۸/۸۳۱۲۵ مورخ ۱۴۰۳/۰۸/۳۰ سرپرست محترم دفتر نظارت و پایش فرآورده های سلامت در خصوص اطلاع رسانی بروزرسانی اطلاعات فراورده دارویی گادوویست جهت بارگذاری در بولتن خبری دفتر نظارت و پایش مصرف فراورده های سلامت جهت استحضار و اطلاع رسانی به حضور ارسال می‌گردد.

دکتر محمود اعتباری
معاون غذا و دارو

رونوشت :

معاون محترم درمان جناب آقای دکتر خوروش جهت استحضار و اقدام لازم

رئیس محترم دانشکده پزشکی جهت استحضار و دستور اقدام لازم

رئیس محترم دانشکده داروسازی و علوم دارویی جناب آقای دکتر مصطفوی جهت استحضار و دستور اقدام لازم

ریاست محترم انجمن داروسازان استان اصفهان جناب آقای دکتر آذربایجانی: جهت استحضار و اطلاع رسانی لازم

رئیس محترم شورای هماهنگی نظام پزشکی جناب آقای دکتر کاشفی: جهت استحضار و اطلاع رسانی لازم

رئیس محترم انجمن شرکتهای پخش استان اصفهان: جهت استحضار و اطلاع رسانی لازم

رئیس محترم داروخانه های آموزشی دانشکده داروسازی و علوم دارویی جناب آقای دکتر حسینی: جهت استحضار و اقدام لازم

سرپرست محترم اورژانس پیش بیمارستانی و مدیر حوادث دانشگاه جناب آقای دکتر زمانی جهت استحضار و اقدام لازم

مسئول محترم روابط عمومی معاونت غذا و دارو جناب آقای فرزین: جهت بارگذاری در صفحه اصلی سایت معاونت

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جمهوری اسلامی ایران
وزارت بهداشت، درمان و آموزش پزشکی

سازمان غذا و دارو
IFDA

شماره: ۶۵۸/۸۳۱۲۵
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پیوست: دارد

جهش تولید با مشارکت مردم

معاونین محترم غذا و دارو دانشگاه/دانشکده های علوم پزشکی، خدمات بهداشتی و درمانی سراسر کشور

موضوع: اطلاع رسانی تغییرات اطلاعات فراورده دارویی گادوویست جهت بارگذاری در بولتن خبری دفتر نظارت و پایش مصرف فراورده های سلامت - معاونتهای غذا و داروی سراسر کشور

با سلام و احترام؛

عطف به نامه شماره۱۶۸/۶۰۱۹۶ مورخ ۱۴۰۳/۸/۱۹ شرکت بایر پارسیان، به استحضار می رساند، تغییرات اعمال شده در اطلاعات فرآورده دارویی (CCDS) داروی گادوبوترول با نام تجاری گادوویست، شامل افزوده شدن عوارض ناخواسته (ARDS) سندرم دیسترس تنفسی حاد و ادم ریه در بخش عوارض ناخواسته فراورده مذکور(فایل پیوست)، خدمتتان ارسال می شود.

خواهشمند است دستور فرمایید، مراتب به اطلاع کلیه مراکز درمانی و دارویی تحت پوشش آن معاونت ارسال شود.

دکتر زهرا جهانگرد
سرپرست دفتر نظارت و پایش مصرف فرآورده های سلامت

رونوشت :

جناب آقای دکتر غلامحسین صادقیان سرپرست محترم اداره کل امور دارو و مواد تحت کنترل
جناب آقای دکتر غلامحسین صادقیان سرپرست محترم دفتر ریاست سازمان غذا و دارو: جهت استحضار و دستور بارگذاری بر روی تارنمای سازمان در بخش بولتن خبری دفتر نظارت و پایش
جناب آقای قربانی متصدی محترم امور دفتری

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Company Core Data Sheet
Gadovist*

Gadobutrol

1.0 mmol/ml, solution for injection

Version 22

Based on GLC decision dated: 11 JUL 2023

For information only

<Section numbering is optional>
<If a statement is valid for <u>one indication</u> only,
this indication is indicated prior to the respective section header. If no indication is mentioned, the chapter is relevant for <u>all indications</u>>

* examples for national trade names: Gadovist, Gadavist

Table of Contents

1. NAME OF THE MEDICINAL PRODUCT

Gadovist 1.0 mmol/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 1.0 mmol gadobutrol (equivalent to 604.72 mg gadobutrol).

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Indication(s)

This medicinal product is for diagnostic use only.

Gadovist is indicated in adults and children of all ages including full-term newborns for contrast enhanced whole body magnetic resonance imaging (MRI) including

- Contrast enhancement in cranial and spinal MRI
- Contrast enhanced MRI of the head and neck region
- Contrast enhanced MRI of the thoracic space
- Contrast enhanced MRI of the breast
- Contrast enhanced MRI of the abdomen (e.g. pancreas, liver and spleen)
- Contrast enhanced MRI of the pelvis (e.g. prostate, bladder and uterus)
- Contrast enhanced MRI of the retroperitoneal space (e.g. kidney)
- Contrast enhanced MRI of the extremities and musculoskeletal system
- Contrast enhancement in Magnetic Resonance Angiography (CE-MRA)
- Contrast enhanced cardiac MRI including assessment of myocardial perfusion under pharmacological stress conditions and viability diagnostics ("delayed enhancement")

4.2 Dosage and method of administration

4.2.1 Method of administration

This medicinal product is for intravenous administration only.

For additional instructions see section ‘Instructions for use / handling’.

Contrast-enhanced MRI can commence immediately afterwards (shortly after the injection depending on the pulse sequences used and the protocol for the examination). Optimal signal enhancement is observed during arterial first pass for CE-MRA and within a period of about

15 minutes after injection of Gadovist for other indications (time depending on type of lesion/tissue).

4.2.2 Dosage regimen

Adults:

A single intravenous injection of 0.1 mmol gadobutrol per kg body weight (equivalent to 0.1 ml Gadovist per kg body weight) is recommended.

A total amount of 0.3 mmol gadobutrol per kg body weight (equivalent to 0.3 ml Gadovist per kg body weight) may be administered at maximum for the central nervous system (CNS) and CE-MRA. A dose of 0.075 mmol gadobutrol per kg body weight (equivalent to 0.075 ml Gadovist per kg body weight) may be administered at minimum for imaging of the CNS.

- Whole Body MRI (except MRA)

In general, the administration of 0.1 ml Gadovist per kg body weight is sufficient to answer the clinical question.

- CE-MRA

Imaging of one field of view:

7.5 ml for body weight less than 75 kg

10 ml for body weight of 75 kg or more

(corresponding to 0.1-0.15 mmol per kg body weight)

Imaging of more than one field of view:

15 ml for body weight less than 75 kg

20 ml for body weight of 75 kg or more

(corresponding to 0.2-0.3 mmol per kg body weight)

4.2.3 Special patient populations

4.2.3.1 Pediatric patients

For children of all ages including full-term newborns the recommended dose is 0.1 mmol gadobutrol per kg body weight (equivalent to 0.1 ml Gadovist per kg body weight) for all indications, see section ‘Indication(s)’.

4.2.3.2 Geriatric patients

4.2.3.3 Patients with hepatic impairment

4.2.3.4 Patients with renal impairment

The elimination of gadobutrol is prolonged in patients with renal impairment. However, to ensure diagnostically useful images no dosage adjustment is recommended (see also section 'Special warnings and precautions for use').

4.3 Contraindications

There are no absolute contraindications to the use of Gadovist.

4.4 Special warnings and precautions for use

4.4.1 Hypersensitivity

Particularly careful risk-benefit assessment is required in patients with known hypersensitivity to Gadovist.

As with other intravenous contrast agents, Gadovist can be associated with anaphylactoid / hypersensitivity or other idiosyncratic reactions, characterized by cardiovascular, respiratory or cutaneous manifestations, and ranging to severe reactions including shock.

The risk of hypersensitivity reactions is higher in case of:

- previous reaction to contrast media
- history of bronchial asthma
- history of allergic disorders

In patients with an allergic disposition the decision to use Gadovist must be made after particularly careful evaluation of the risk-benefit ratio.

Most of these reactions occur within half an hour of administration.

Therefore, post-procedure observation of the patient is recommended.

Medication for the treatment of hypersensitivity reactions as well as preparedness for institution of emergency measures are necessary.

Delayed reactions (after hours up to several days) have been rarely observed (see section 'Undesirable effects').

4.4.2 Impaired renal function

Prior to administration of Gadovist all patients should be screened for renal dysfunction by obtaining a history and/or laboratory tests.

In patients with severely impaired renal function the benefits must be weighed carefully against the risks, since contrast medium elimination is delayed in such cases.

Because Gadobutrol is renally excreted sufficient period of time for elimination of the contrast agent from the body prior to any re-administration in patients with renal impairment should be ensured. Usually, complete recovery in the urine was seen in patients with mild or moderate renal impairment within 72 hours. In patients with severely impaired renal function at least 80 % of the administered dose was recovered in the urine within 5 days.

Gadovist can be removed from the body by hemodialysis. After 3 dialysis sessions approx. 98 % of the agent are removed from the body. For patients already receiving hemodialysis at the time of Gadovist administration, prompt initiation of hemodialysis following the administration of Gadovist should be considered, in order to enhance the contrast agent's elimination.

There have been reports of nephrogenic systemic fibrosis (NSF) (see section 'Undesirable effects') associated with the use of gadolinium-containing contrast agents including Gadovist in patients with

- acute or chronic severe renal impairment (GFR < 30 ml/min/1.73m^2) or
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

Therefore, Gadovist should only be used in these patients after careful risk/benefit assessment.

4.4.3 Seizure disorders

As with other gadolinium-chelate-containing contrast media, special precaution is necessary in patients with a low threshold for seizures.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions studies with other medicinal products have been conducted.

4.6 Pregnancy and lactation

4.6.1 Pregnancy

For gadobutrol no clinical study data on exposed pregnancies are available.

Animal studies at clinically relevant doses have not shown reproductive toxicity after repeated administration.

The potential risk for humans is unknown.

Gadovist should not be used during pregnancy unless clearly necessary.

4.6.2 Lactation

It is unknown whether gadobutrol is excreted in human milk.

There is evidence from non-clinical data that gadobutrol is excreted into breast milk in very small amounts (less than 0.1% of the dose intravenously administered) and the absorption via the gastrointestinal tract is poor (about 5% of the dose orally administered were excreted in the urine).

At clinical doses, no effects on the infant are anticipated and Gadovist can be used during breastfeeding.

4.7 Effects on ability to drive or use machines

4.8 Undesirable effects

4.8.1 Summary of the safety profile

The overall safety profile of Gadovist is based on data from more than 6,300 patients in clinical trials, and from post-marketing surveillance.

The most frequently observed adverse drug reactions (≥ 0.5 %) in patients receiving Gadovist are headache, nausea, and dizziness.

The most serious adverse drug reactions in patients receiving Gadovist are cardiac arrest, acute respiratory distress syndrome / pulmonary edema and severe anaphylactoid reactions.

Delayed allergoid or other idiosyncratic reactions (hours later up to several days) have been rarely observed.

Most of the undesirable effects were of mild to moderate intensity.

4.8.2 Tabulated list of adverse reactions

The adverse drug reactions observed with Gadovist are represented in the table below. They are classified according to System Organ Class. The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Adverse drug reactions from clinical trials are classified according to their frequencies. Frequency groupings are defined according to the following convention: common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1,000 to < 1/100; rare: ≥ 1/10,000 to < 1/1,000. The adverse drug reactions identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under ‘not known’.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse drug reactions reported in clinical trials or during post-marketing surveillance in patients treated with Gadovist

System Organ Class	Common	Uncommon	Rare	Not known
Immune system disorders		Hypersensitivity / anaphylactoid reaction[*] [#] (e.g. anaphylactoid shock[§], circulatory collapse[§], respiratory arrest[§], bronchospasm[§], cyanosis[§], oropharyngeal swelling[§], laryngeal edema[§], hypotension, blood pressure increased[§], chest pain[§], urticaria, face edema, angioedema[§], conjunctivitis[§], eyelid edema, flushing, hyperhidrosis[§], cough[§], sneezing[§], burning sensation[§], pallor[§])		
Nervous system disorders	Headache	Dizziness Dysgeusia Paresthesia	Loss of consciousness* Convulsion Parosmia	
Cardiac disorders			Tachycardia Palpitations	Cardiac arrest*
Respiratory, thoracic and mediastinal disorders		Dyspnea*		Acute Respiratory Distress Syndrome (ARDS)* Pulmonary edema*
Gastrointestinal	Nausea	Vomiting	Dry mouth	

System Organ Class	Common	Uncommon	Rare	Not known
disorders				
Skin and subcutaneous tissue disorders		Erythema Pruritus (including generalized pruritus) Rash (including generalized, macular, papular, pruritic rash)		Nephrogenic Systemic Fibrosis (NSF)
General disorders and administration site conditions		Injection site reaction[0] Feeling hot	Malaise Feeling cold	

* There have been reports of life-threatening and/or fatal outcomes from this ADR

[#] None of the individual symptoms ADRs listed under hypersensitivity / anaphylactoid reaction identified in clinical trials reached a frequency greater than rare (except for urticaria)

[§] Hypersensitivity / anaphylactoid reactions identified only during post-marketing surveillance (frequency not known)

[0] Injection site reactions (various kinds) comprise the following terms: Injection site extravasation, injection site burning, injection site coldness, injection site warmth, injection site erythema or rash, injection site pain, injection site hematoma

4.9 Overdose

Single doses of gadobutrol as high as 1.5 mmol gadobutrol/kg body weight were tolerated well.

In case of inadvertent overdosage, cardiovascular monitoring (including ECG) and control of renal function are recommended as a measure of precaution.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

5.2 Pharmacokinetic properties

5.3 Preclinical safety data

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1 N hydrochloric acid
Calcobutrol sodium
Trometamol
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

After the vial/bottle has been opened or the prefilled syringe or prefilled cartridge has been prepared for use, Gadovist remains stable for 24 hours at 20 to 25 °C and must be discarded thereafter.

6.4 Special precautions for storage

6.5 Nature and contents of container

6.6 Instructions for use / handling

6.6.1 Visual inspection

This medicinal product should be visually inspected before use.

Gadovist should not be used in case of severe discoloration, the occurrence of particulate matter or a defective container.

6.6.2 Vials

Gadovist should only be drawn into the syringe immediately before use.

The rubber stopper should never be pierced more than once.

Any contrast medium solution not used in one examination must be discarded.

6.6.3 Prefilled syringes

The prefilled syringe must be taken from the pack and prepared for the injection immediately before the administration.

The tip cap should be removed from the prefilled syringe immediately before use.

Any contrast medium solution not used in one examination must be discarded.

6.6.4 Large volume container

In addition, the following applies to use of the 100 ml infusion bottle containing 65 ml:

Instructions of the device manufacturer must be followed.

For further information see also section ‘Shelf life’.

6.6.5 Prefilled cartridges

Administration of contrast media should be performed by qualified personnel with the appropriate procedures and equipment.

Sterile technique must be used in all injections involving contrast media.

Instructions of the device manufacturer must be followed.

Any contrast medium solution not used in one examination must be discarded.

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Case Report

Delayed anaphylaxis due to gadolinium- A rare clinical scenario

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ABSTRACT

Acute respiratory distress syndrome is a sudden in onset, diffuse inflammatory form of lung injury which may be associated with a variety of etiologies such as pneumonia, sepsis, aspiration, and severe trauma. Prompt recognition and treatment of acute respiratory distress syndrome is critical to reduce the associated high mortality. Severe lung injury presenting as acute respiratory distress syndrome secondary to gadolinium contrast media (gadobutrol) is rarely reported. We describe an interesting case of a 47-year-old woman who presented to the emergency department with acute respiratory failure after gadolinium administration. She was diagnosed with acute respiratory distress syndrome, was admitted to the intensive care unit due to requiring mechanical ventilation. Her condition improved with epinephrine and steroids and she was successfully extubated and discharged from the hospital in one week.

Introduction

The contrast agent gadolinium has been in use for imaging studies especially magnetic resonance imaging for more than 30 years due to its high reliability and low rates of adverse effects. Gadobutrol is a second-generation non-ionic macrocyclic gadolinium-based contrast agent with high thermostability. Adverse reaction due to gadobutrol such as noncardiogenic pulmonary edema is extremely rare [1]. We present an interesting case of acute respiratory distress syndrome associated with the use of gadobutrol.

Case Description

A 47-year-old female (weighted 75.5 kilogram) with previous medical history of hypothyroidism on levothyroxine only, presented to the emergency department (ED) for acute shortness of breath and cyanosis of the lips. The patient had an MRI of the breast with gadolinium (gadovist 7 milliliters intravenously) done in outpatient clinic two hours before she presented to the ED. She had no relevant history of drug or seasonal allergies. She was never exposed to dye or contrast agents before this event.

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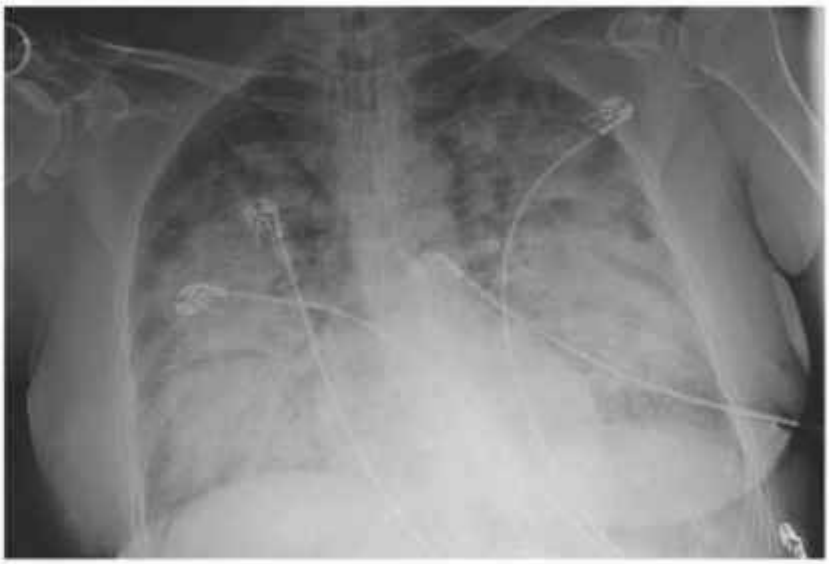

Fig. 1 – Bilateral ground glass opacities noted on Chest X-ray at the time of admission.

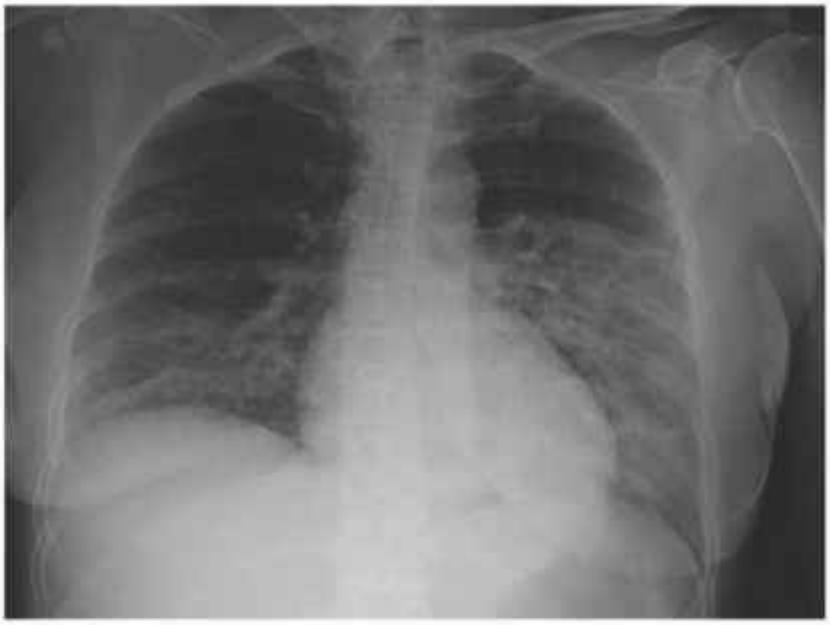

Fig. 2 – Resolution of ground glass opacities on Chest X-ray at the time of discharge.

When she was brought to the ED, she was short of breath at rest and on exertion. She was in mild distress, felt nauseous, dizzy and was noted to have bilateral rales on exam. Her fist vital signs included blood pressure (118/70 mmHg), heart rate 128 beats/minute, temperature (94.9-degree Fahrenheit), respiratory rate 26 and oxygen saturation of 96% on 15-liter/minute face mask. She received intravenous diphenhydramine and methyl prednisone with partial relief. Her repeat saturating pulse oxygen in the ED was 80% on 3-liter/minute oxygen supplementation. The chest X-ray (Figs. 1-2) showed bilateral diffuse ground glass opacities. She was placed on bilevel positive airway pressure (BiPap) machine for 1 hour in the ED for symptomatic relief. However, she continued to be tachypneic, hypoxic and became hypotensive to systolic blood pressure 90 mmHg.

The patient had to intubated and placed on mechanical ventilation due to worsening respiratory status and was started on epinephrine drip. She was managed for presumed

diagnosis of acute respiratory distress syndrome secondary to anaphylaxis from gadolinium. A full workup was undertaken to rule out other possible causes attributing to her condition. Her transthoracic echocardiogram and b-natriuretic peptide were in normal range. She had been afebrile throughout her hospital stay and pan-cultures were negative for any growth. Her Covid-19 PCR was negative twice and covid-19 antibodies were also negative. No other organ failure was observed; there were no findings suggesting anaphylaxis such as rash, wheezing, or abdominal symptoms. She was kept on epinephrine drip for about 12 hours and subsequently weaned off. The patient eventually got extubated on day four of the hospital stay and was discharged on day seven with epinephrine pen.

Discussion

Gadobutrol is a commonly used second-generation non-ionic macrocyclic gadolinium-based contrast agent (GBCA) for imaging studies. It has a higher ionic concentration than other MRI contrast agents, which allows testing with smaller doses [2]. GBCA administered to patients with decreased renal function can trigger nephrogenic systemic fibrosis; thus, use in patients with chronic renal failure is not usually recommended [3]. Although, GBCA is associated with lower rates of hypersensitivity reactions as compared to other iodine-based contrast agents, there has been some increase in number of reported events noted in medical literature likely due to widespread use of gadolinium [4,5].

Adverse reactions because of gadobutrol administration are characterized by their immediate onset; commonly occurring within the first 5 minutes of administration in 82.4% cases and in the first 10 minutes of administration in 95.7% cases [6]. Commonly reported adverse reactions include nausea, vomiting, urticaria, flushing, tachycardia, wheals, dizziness, and dyspnea. However, acute respiratory distress syndrome (ARDS) and anaphylactic reactions secondary to gadobutrol administration is a rarely described phenomenon in medical literature which may result in pulmonary edema. Pulmonary edema can be cardiogenic or non-cardiogenic; the latter occurs as a result of increased microvascular permeability and alveolar fluid infiltration. This drug-induced ARDS is hypothesized to occur through chemical injury to the vascular endothelium which results in hypoxia and pulmonary vascular resistance from accumulation of protein-rich substances in the alveoli [7]. The exact component of gadobutrol responsible for such severe hypersensitivity reaction and ARDS is unknown. However, the endothelial injury triggers the activation of complement system as well which play a role in promoting pulmonary edema [8,9].

In our case, the patient started having onset symptoms approximately 1-2 hour after administration of gadolinium. She was diagnosed with ARDS and treated with epinephrine, steroids, and artificial mechanical ventilation. The hospital course was uneventful, and she was successfully extubated and discharged in a week on epinephrine-pen. There are only a few reported cases of gadolinium induced severe reactions [1,7,10-12]. Some of these reactions are delayed in onset, suggesting that gadobutrol-induced ARDS may occur by a mechanism other than an immediate sensitivity reaction, such as anaphylaxis. Although our patient also showed delayed reactivity response to gadobutrol, given the symptoms of cyanosis, profound dyspnea and significant respiratory failure, we would include this clinical case in spectrum of anaphylactic reaction.

Conclusion

In this case report, we describe an interesting case of anaphylactic reaction to gadobutrol dye used in magnetic resonance imaging. Although gadolinium is very safe to use, caution should be practiced for allergic reactions and the patients should be advised about the possibility of delayed allergic symptoms which may occur 1-2 hours after its use.

Conset

I, Shamsuddin Anwar, as a corresponding author of this manuscript solemnly declare that no identifying information has been revealed or presented in the manuscript. The patient was informed and consented for the submission of the case report in the journal.

Declaration

I, Shamsuddin Anwar, as a corresponding author of this manuscript would like to declare that none of the authors have any conflict of interests in writing and submission of the manuscript. We have not received any funding or compensation of any form in writing of the article.

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Endocrine Abstracts

Society for Endocrinology BES 2011

Birmingham, UK
11 April 2011 - 14 April 2011
Society for Endocrinology
British Endocrine Societies

Endocrine Abstracts (2011) **25** P61

Life-threatening adverse reaction following pituitary MRI

Katerina Achilleos, Tehmina Irani & James Ahlquist

Southend Hospital, Westcliff on Sea, Essex, UK.

Pituitary MRI is widely used in endocrine practice, and is regarded as entirely safe. We report here a life-threatening outcome from a routine pituitary MRI scan.

A 23-year-old female with a 3-year history of microprolactinoma confirmed by MRI underwent a routine repeat MRI scan with gadolinium. During injection of Gadovist she experienced minimal chest tightness which rapidly resolved. Four hours after the injection she rapidly became very breathless. On admission to hospital she was shocked, profoundly breathless, with cyanosis, hypotension and marked hypoxia (HR 162 bpm, BP 72/50 mmHg, PaO_2 7 kPa despite FiO_2 60%); there were diffuse crepitations throughout both lung fields and no signs of cardiac disease or angioedema. CXR showed bilateral perihilar alveolar shadowing, indicating pulmonary oedema/ARDS.

She was treated with high-flow oxygen, adrenaline, hydrocortisone, chlorpheniramine and furosemide. She remained critically ill and was admitted to ITU, where she required inotropes and CPAP non-invasive ventilation for persistent acute respiratory failure. Echocardiogram confirmed normal cardiac function. She made a rapid recovery and was discharged home well 2 days later. She subsequently recalled that she had felt slightly unwell after her first MRI scan 3 years earlier.

Acute lung injury has not previously been reported after gadolinium administration. Gadolinium-induced serious adverse reactions are extremely rare (1–3 per million administered doses). Gadovist is a modern contrast agent regarded as having a very low potential for anaphylactoid reactions; it includes a macrocyclic chelate which is thought to give less risk of gadolinium toxicity than older agents with a linear chelate such as Omniscan. However, macrocyclic gadolinium agents may be associated with a higher frequency of allergic reactions.

Pituitary disease is rarely fatal. Endocrinologists should be aware that pituitary MRI carries a small risk of iatrogenic adverse reaction which may be life-threatening.

Endocrine Abstracts (2011) **25** P61

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LETTER OF APPROVAL

Product Name	MAH	Product Number
Gadovist 1,0 mmol/ml Injektionslösung	Bayer Vital GmbH	2140252
Gadovist 1.0 mmol/ml Injektionslösung in Fertigspritzen/Patronen	Bayer Vital GmbH	2149628
GadovistAuto 1,0 mmol/ml Injektionslösung in einer Fertigspritze	Bayer Vital GmbH	2198640
GadovistManuell 1,0 mmol/ml Injektionslösung in einer Fertigspritze	Bayer Vital GmbH	2198641

Variation: DE/H/xxxx/WS/1511

12/09/2024

The a. m. variation application is hereby nationally approved by the Federal Institute for Drugs and Medical Devices (BfArM); the procedure is closed. The approved changes are:

C.I.4. Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.

With this variation the MAH aims to update Section 4.8 of the SmPC and PIL respectively with inclusion of acute respiratory distress sydrome + pulmonary oedema in system organ class " respiratory thoracic and mediastinal disorders".

Date of Approval: 03.09.2024

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Is This Anaphylaxis? ARDS and Shock from Gadolinium Based Contrast

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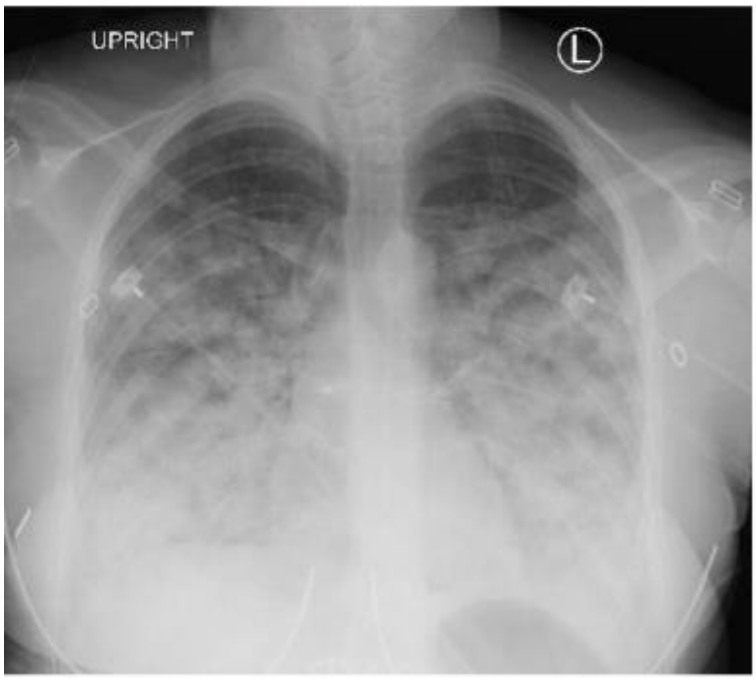
INTRODUCTION: Adverse reactions to gadolinium-based contrast agents (GBCAs) are rare with rates as low as 0.01%. They are not well recognized or understood, which can make their management challenging. Here we describe an unusually severe case of acute respiratory distress syndrome (ARDS) with shock and disseminated intravascular coagulopathy (DIC) related to a GBCA. CASE: A 25 year-old woman with a history of Crohn's disease was in her usual state of health until she presented to the Emergency Department with two episodes of syncope ninety minutes after an outpatient MR Enterography. Prior to the scan, she received 6ml of Gadavist (gadobutrol at 1mmol/ml). In the ED she was hypotensive to 87/59mmHg and wheezing with progressive hypoxemia requiring HFNC 30L FiO2 100%. Arterial blood gas showed pH 7.34, PaCO2 23mmHg, PaO2 146mmHg with a PaO2/FiO2 ratio of 146. Chest radiograph showed bilateral alveolar infiltrates. B-type natriuretic peptide and echocardiogram were normal. She had nausea and emesis, but did not have rashes or swelling. Epinephrine 0.3mg IM was given twice along with methylprednisolone 125mg IV followed by an epinephrine infusion. Despite these measures, she developed worsening hypoxemia, shock, lactic acidosis and DIC requiring intubation, norepinephrine, vasopressin, and dialysis for metabolic acidosis. Tryptase at this time was normal, though was drawn about 23 hours after onset of symptoms. She clinically improved, was extubated on day 4, and discharged home on day 9 without residual complications.

DISCUSSION: Gadobutrol is generally well tolerated with minimal side effects reported in the literature. ARDS secondary to contrast enhanced MRI is a rare entity. To our knowledge, there are only seven published case reports, with varying degrees of severity, duration of symptoms and clinical features. Interestingly, most cases resolved within the duration of days. Two cases demonstrated anaphylaxis to other MRI contrast agents. These patients were exposed to these agents for the first time as in our patient. This raises concerns about whether the underlying mechanism of the response is related to the structure of the molecule rather than an IgE mediated response. No other case in the literature was complicated by multiorgan dysfunction and DIC. This case highlights the importance of characterization of the underlying pathophysiology and therefore management of the disease, as well as being wary of the safety profile of the contrast agent.



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Location: San Francisco, CA; USA
Date: 5/13/2022

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European Review for Medical and Pharmacological Sciences 2012; 16(4 Suppl): 110-112

Magnetic resonance imaging contrast agent related pulmonary edema: a case report

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Abstract. – Gadobutrol is a contrast agent often used during magnetic resonance imaging (MRI). The agent has several side effects, some of which can be serious. It has extremely rare life-threatening systemic complications, which can lead to bronchospasm, hypersensitivity reactions and cardiovascular arrest. However, there is no data available on the development of noncardiogenic pulmonary edema following use of gadobutrol. This paper examines the case of a 37-year-old male patient reported to have developed noncardiogenic pulmonary edema after intravenous injection of gadobutrol during MRI.

Key Words:
Contrast agents, Gadobutrol, Magnetic resonance imaging, Noncardiogenic pulmonary edema.

Introduction

Gadobutrol has a safety profile comparable to other Gadolinium-based MRI contrast agents (MRI-ca)[1]. The agent is often preferred as it provides superior quality MRI conditions[2]. Its plasma half-life is about 90 minutes. After intravenous (i.v.) administration, its plasma level rapidly peaks within minutes, and it is then excreted renally[3].

Although side effects are similar to other gadolinium-based agents, these are usually a mild or moderate[4]. The most common are headache, dizziness and nausea. Dyspnea, urticaria, and anaphylactic reactions rarely occur[4]. In adults, gadolinium-based MRI-ca related hypersensitivity reactions are seen in 0.07% of patients. Seventy-four percent of these reactions are mild[5]. Very rarely, severe anaphylaxis can be encountered[6]. Reactions can occur rapidly (< 1 hour), or slowly (> 1 h)[6]. Acute reactions usually manifest themselves as anaphylaxis. In such situations, fast and effective treatment can be life saving[6]. Although gadolinium related reactions are well known, there are no available information about gadolinium attributable pulmonary damage. This paper presents a case of noncardiogenic pulmonary edema, developed after i.v. injection of gadobutrol during MRI.

Case

A 37-year-old male patient with a complaint of lumbalgia was admitted to our Neurology Clinic. During the spinal MRI procedure, intravenous gadobutrol was given by cephalic vein (solution Gadovist, Bayer Schering Pharma AG, Germany) (14 ml).

Following injection of the MRI-ca, the patient developed severe dyspnea, cyanosis, and loss of consciousness. Nasal oxygen was initiated. Methylprednisolone (i.v. 125 mg) was administered and the patient was transferred to the intensive care unit (ICU). He had no prior history of MRI-ca exposure, drug allergies, atopy or systemic disease. He was unconscious upon arrival to the ICU and had bradypnea, cyanosis, and absent arterial pulsation.

Airway patency was rapidly secured by tracheal intubation and connected to a manuel bag-valve system with oxygen at a rate of 10 L/min. Although monitored heart rate was 110 BPM, there were no pulses at peripheral arteries and arterial blood pressure could not be measured. External cardiac compression was started. Adrenaline 1 mg i.v. was given. An arterial blood gas analysis was pH 7.16; $PaCO_2$: 69 mmHg; PaO_2: 24 mm Hg.

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To correct cardiovascular collapse, fluid replacement and dopamine (10 µg/kg/ min) infusion was started. Approximately 1500 ml of fluid infusion was given over a 15 minute period. Following inotropic support, an intraarterial line was placed and the blood pressure was recorded as 65/27 mmHg and the peripheral arterial saturation was 77%. Cardiac compressions were terminated and the patient was connected to mechanical ventilator on SIMV mode. The ventilator parameters were adjusted as follows: FiO_2: 100%; frequency: 16/dk; PEEP: 5 cm H_2O; and tidal volume: 7 ml/kg.

Despite the maximally used dose of dopamine and 4 mg of adrenaline, invasive blood pressure value was not high enough. Staff administered a 10 µg/min infusion of noradrenaline (8 µg/mL). The ECG showed sinus rhythm and T wave inversions in the inferior and lateral leads. Transthoracic echocardiogram showed normal left ventricule and valve function. Diffuse rales were heard during pulmonary auscultation.

A chest radiograph showed an increase in pulmonary vascularity (Figure 1). Biochemical laboratory values were measured in the blood as follows: CK: 303 U/L; CK-MB: 88 U/L; troponin I: 11.4 ng/ml; Ca: 6.9 mmol/L; WBC: 31.7 K/uL; and NEU: 30.1 K/uL. Serum potassium was 2.4 mmol/L and a potassium infusion was initiated. Subsequent values indicated 2 mmol/L and 1.6 mmol/L and the concentration of potassium in the infusion was increased. Arterial blood gas after one hour on 100% oxygen indicated the chest radiograph showed significant improvement and the t-wave inversion reversed. CVP was 11 cmH_2O, and there was no urinary output detected within the first hour of ICU admission. After one hour, urine output started at a rate of 110 ml/h, and increased over several hours to an average rate of 300-400 ml/h. FiO_2 was 100% at the end of the first hour. The result of blood gas analysis at first hour with 100% FiO_2 as follows pH: 7.25 mmHg, PaO_2: 122 mmHg $PaCO_2$: 53 mmHg. FiO_2 was gradually reduced according to the values of repeated blood gas tests.

Four hours after ICU admission, with 60% FiO_2, the results obtained as pH: 7.31, PaO_2: 275 mmHg, $PaCO_2$: 43 mmHg, HCO_3: 21.7 mmol/L. Dopamine and noradrenaline infusions were tapered off as arterial blood pressure stabilized at around 130/75 mm Hg. Control chest X-rays showed almost recovery (Figure) and T wave inversion in ECG returned to normal. Recovery of the patient based on respiratory and hemodynamic parameters necessitated changing the mode of ventilation to CPAP. The patient was extubated after 12 hours in the ICU. The control values of serum cardiac markers (such as creatine kinase myocardial band [CK-MB] and troponin I) gradually decreased. A day after admission, the patient was transferred to the Cardiology Service and observed for three days for complications. He was discharged without sequelae.

Discussion

Gadobutrol can have serious side effects, such as dyspnea, anaphylactic reactions and excessive hypotension, but these are very rare[7]. Despite evidence of anaphylactic shock through the use of

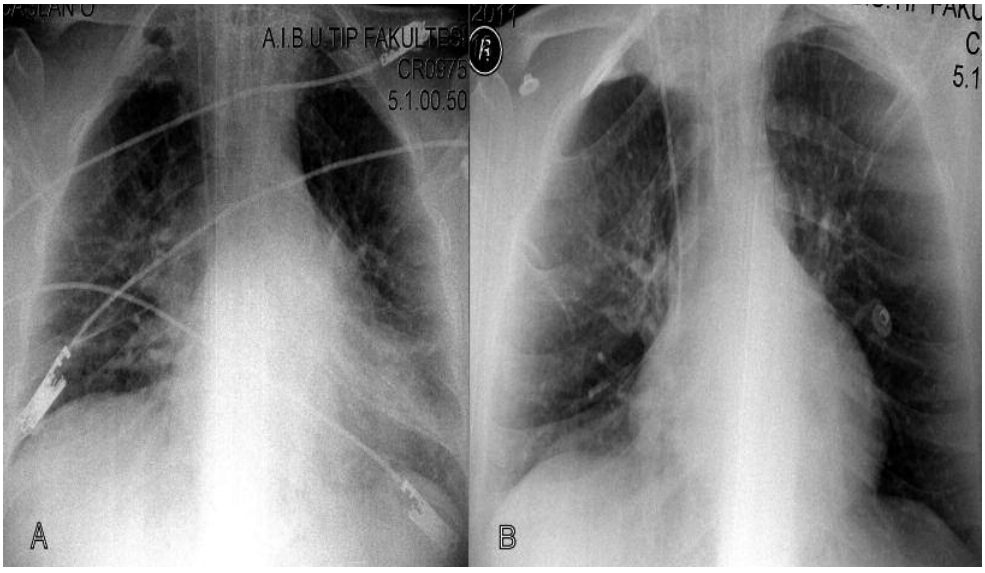

Figure 1. Chest roentgenogram. ***A,*** The image shows increased pulmonary vascularity. The X ray obtained 30 min after ICU admission. ***B,*** The X ray after 12 hours of ICU admission.

gadobutrol as reported in the literature, we found no reports of the development of pulmonary edema with this agent. Therefore, this paper represents the first case of this complication. Pulmonary edema is generally seen in two different forms; noncardiogenic and cardiogenic[8]. Noncardiogenic pulmonary edema (NCPE) is leakage of fluid as a result of increased microvascular permeability[9]. How MRI contrast agents cause pulmonary edema is not known. It has been suggested that it is the result of widespread endothelial damage induced by activation of the complement system, or as a direct irritant effect of the drug in the lung[1,8,9].

Gadobutrol has been used worldwide in approximately 5.7 million patients between 1998 and 2010. Of these, 1175 have developed side effects. Serious reactions were reported in 309 cases. These are cardiac and respiratory arrest, anaphylactoid shock, and nephrogenic systemic fibrosis[7]. Forstinga et al[10] published an observational study of 14,299 patients. Results of the study showed nausea and vomiting to be the most frequent side effect (0.31%), followed by urticaria (0.08%), and other skin lesions (0.07%). Only two patients (0.01%) presented serious side effects, one of which was anaphylactic reaction, while the other was swelling and itching of the throat.

In our case, rapid development of dyspnea and cyanosis immediately after administration of i.v. gadobutrol suggests NCPE. Rales were present in the lungs, the PaO_2/FiO_2 rate was less than 200, there was increased pulmonary vascular congestion on chest X-ray, and there was rapid response to treatment; all supporting NCPE. Gadobutrol associated skin lesions have rarely been reported[4,10]. In our patient, excessive hypotension, despite the lack of skin lesions, suggests severe anaphylactic reaction. The patients' diagnosis was anaphylactic shock with noncardiogenic pulmonary edema and provides the first case in the current literature.

In this case, severe hypokalemia was observed. There is no information that gadobutrol may cause this situation. However, in an *in vitro* study, hERG (human Ether-a-go-go) mediated dose-dependent inhibition of potassium current has been reported[11]. We observed hypopotassemia rather than hyperpotassemia, which usually accompanies acidosis. This phenomenon can be explained by inhibition of potassium current. This effect can also be thought to play a role in observed ECG changes in the patient. We suggest that the raised values of serum cardiac markers were the result of cardiac massage, because of normal ventricular wall motion in transthoracic echocardiography.

In conclusion, anaphylactic shock with noncardiogenic pulmonary edema after the use of gadobutrol is presented in this paper. As this is the first case in the literature, we suggest anaphylactic shock and noncardiogenic pulmonary edema must be kept in mind during MRI. Additionally, as in this case, accompanied hypopotassemia requires analysis and should be investigated in terms of gadobutrol attributable arrests, and, in particular, hERG mediated potassium current inhibition.

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Report Name:	RA Report 008b – Report on CCDS Change History Filter by product
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Export By:	damiantomasz.dziura.ext@bayer.com
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	Event Product > Product in "Gadovist, Solution for injection, 1 mmol per 1 ml, Gadovist, Solution for injection in pre-filled syr, 1 mmol per 1 ml"
	Event > Event Object Type equals "CCDS/CIFU Event"
	Events has at least one "Event Product"
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Filters:	Event > GLC Decision Date is not blank
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Domain Name:	bayer

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CCDS/CIFU Event-001235	REC-00031825		11 Jul 2023	Gadovist CCDS/CIFU Update Version 22 Inclusion of Acute Respiratory Distress Syndrome (ARDS) and Pulmonary Edema (PE) to section 4.8 under SOC 'Respiratory, thoracic and mediastinal disorders'	4	Minor	CCDS, CCPI	aCCDS 22 Gadovist (v1.0)	aCCPI 22 Gadovist (v1.0)		CCDS/CIFU/Label-Change-0007808	Adverse drug reactions	CCDS #22; Inclusion of Acute Respiratory Distress Syndrome (ARDS) and Pulmonary Edema (PE) to section 4.8 under SOC 'Respiratory, thoracic and mediastinal disorders'	Gadovist Labeling Binder CCDS Update version 21 to 22 (v1.1)	Gadovist Labeling Binder CCDS Update version 21 to 22	Labeling Binder	EV-PR-0060859	Gadovist, Solution for injection, 1 mmol per 1 ml	Gadobutrol	4007819, Gadobutrol
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CCDS/CIFU Event-000828	REC - 00015015		08 Mar 2019	CCDS # 20; no Priority GLC decision date 2019-03-08	None	None					CCDS/CIFU/Label-Change-0005034	Pharmacodynamic properties	CCDS # 20; no Priority GLC decision date 2019-03-08				EV-PR-0010660	Gadovist, Solution for injection in pre-filled syr, 1 mmol per 1 ml	Gadobutrol	
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											CCDS/CIFU/Label-Change-0005365	Pharmacokinetic properties	CCDS 18 GLC decision date 2012-06-12							
											CCDS/CIFU/Label-Change-0006405	Warnings and precautions	CCDS 18 GLC decision date 2012-06-12							
CCDS/CIFU Event-000581	REC - 00018441		12 Jun 2012	Label No. 4998 update to CCDS 18 - split submission of sections 4.2 upon HA request in Brazil No priority-4.2 Labeling – Dosage and administration GLC Decision date: 2012-06-12	None	None					CCDS/CIFU/Label-Change-0001012	Dosage and method of administration	Label No. 4998 update to CCDS 18 - split submission of sections 4.2 upon HA request in Brazil No priority-4.2 Labeling – Dosage and administration GLC Decision date: 2012-06-12				EV-PR-0017020	Gadovist, Solution for injection, 1 mmol per 1 ml	Gadobutrol	4007819, Gadobutrol
CCDS/CIFU Event-000084	REC - 00003562		13 Apr 2010	CCDS 16	3	Important					CCDS/CIFU/Label-Change-0001165	Dosage and method of administration	CCDS 16				EV-PR-0025985	Gadovist, Solution for injection in pre-filled syr, 1 mmol per 1 ml	Gadobutrol	
											CCDS/CIFU/Label-Change-0001773	Instructions for use / handling	CCDS 16				EV-PR-0025986	Gadovist, Solution for injection, 1 mmol per 1 ml	Gadobutrol	4007819, Gadobutrol
											CCDS/CIFU/Label-Change-0003763	Other	CCDS 16							
											CCDS/CIFU/Label-Change-0004923	Overdose	CCDS 16							
											CCDS/CIFU/Label-Change-0005149	Pharmacodynamic properties	CCDS 16							
											CCDS/CIFU/Label-Change-0005352	Pharmacokinetic properties	CCDS 16							
											CCDS/CIFU/Label-Change-0005511	Preclinical safety data	CCDS 16							
											CCDS/CIFU/Label-Change-0006308	Warnings and precautions	CCDS 16							
CCDS/CIFU Event-000108	REC - 00002518		11 Sep 2007	14th CCDS for Gadovist, GLC priority 3b	3	Important					CCDS/CIFU/Label-Change-0003577	Other	14th CCDS for Gadovist, GLC priority 3b				EV-PR-0022672	Gadovist, Solution for injection in pre-filled syr, 1 mmol per 1 ml	Gadobutrol	
											CCDS/CIFU/Label-Change-0006229	Warnings and precautions	14th CCDS for Gadovist, GLC priority 3b				EV-PR-0022673	Gadovist, Solution for injection, 1 mmol per 1 ml	Gadobutrol	4007819, Gadobutrol
CCDS/CIFU Event-000902	REC - 00002040		26 Jun 2006	1st CCDS for Gadovist							CCDS/CIFU/Label-Change-0000290	Adverse drug reactions	1st CCDS for Gadovist				EV-PR-0019926	Gadovist, Solution for injection in pre-filled syr, 1 mmol per 1 ml	Gadobutrol	
											CCDS/CIFU/Label-Change-0000739	Contraindications	1st CCDS for Gadovist				EV-PR-0019927	Gadovist, Solution for injection, 1 mmol per 1 ml	Gadobutrol	4007819, Gadobutrol
											CCDS/CIFU/Label-Change-0001749	Instructions for use / handling	1st CCDS for Gadovist							
											CCDS/CIFU/Label-Change-0003410	Other	1st CCDS for Gadovist							
											CCDS/CIFU/Label-Change-0006132	Warnings and precautions	1st CCDS for Gadovist							
CCDS/CIFU Event-000791	REC - 00001352		08 Jun 2004	CCT-change; the CCT-chapter 4.4 precautions/warnings was revised only for Gadovist 1.0 whereas all other changes refer to both strengths.							CCDS/CIFU/Label-Change-0002691	Other	CCT-change; the CCT-chapter 4.4 precautions/warnings was revised only for Gadovist 1.0 whereas all other changes refer to both strengths.				EV-PR-0008160	Gadovist, Solution for injection in pre-filled syr, 1 mmol per 1 ml	Gadobutrol	
											CCDS/CIFU/Label-Change-0004867	Overdose	CCT-change; the CCT-chapter 4.4 precautions/warnings was revised only for Gadovist 1.0 whereas all other changes refer to both strengths.				EV-PR-0008162	Gadovist, Solution for injection, 1 mmol per 1 ml	Gadobutrol	4007819, Gadobutrol
											CCDS/CIFU/Label-Change-0005431	Preclinical safety data	CCT-change; the CCT-chapter 4.4 precautions/warnings was revised only for Gadovist 1.0 whereas all other changes refer to both strengths.							
											CCDS/CIFU/Label-Change-0005801	Warnings and precautions	CCT-change; the CCT-chapter 4.4 precautions/warnings was revised only for Gadovist 1.0 whereas all other changes refer to both strengths.							
CCDS/CIFU Event-001058	REC - 00000539		24 Apr 2002	CCT change							CCDS/CIFU/Label-Change-0002216	List of excipients	CCT change				EV-PR-0032979	Gadovist, Solution for injection in pre-filled syr, 1 mmol per 1 ml	Gadobutrol	
											CCDS/CIFU/Label-Change-0004189	Other	CCT change				EV-PR-0032981	Gadovist, Solution for injection, 1 mmol per 1 ml	Gadobutrol	4007819, Gadobutrol
CCDS/CIFU Event-000423	REC - 00000324		25 Apr 2001	CCT change							CCDS/CIFU/Label-Change-0001133	Dosage and method of administration	CCT change				EV-PR-0025199	Gadovist, Solution for injection in pre-filled syr, 1 mmol per 1 ml	Gadobutrol	
											CCDS/CIFU/Label-Change-0001771	Instructions for use / handling	CCT change				EV-PR-0025201	Gadovist, Solution for injection, 1 mmol per 1 ml	Gadobutrol	4007819, Gadobutrol
											CCDS/CIFU/Label-Change-0002202	List of excipients	CCT change							
											CCDS/CIFU/Label-Change-0004922	Overdose	CCT change							
											CCDS/CIFU/Label-Change-0005350	Pharmacokinetic properties	CCT change							
											CCDS/CIFU/Label-Change-0005508	Preclinical safety data	CCT change							
											CCDS/CIFU/Label-Change-0006271	Warnings and precautions	CCT change							

												CCDS/CIFU/Label-Change-0001488	Incompatibilities	CCT change				EV-PR-0023400	Gadovist, Solution for injection in pre-filled syr, 1 mmol per 1 ml	Gadobutrol	
												CCDS/CIFU/Label-Change-0002198	List of excipients	CCT change				EV-PR-0023402	Gadovist, Solution for injection, 1 mmol per 1 ml	Gadobutrol	4007819, Gadobutrol
CCDS/CIFU Event-000690	REC - 00000282		25 Apr 2000	CCT change								CCDS/CIFU/Label-Change-0003639	Other	CCT change							
												CCDS/CIFU/Label-Change-0005121	Pharmacodynamic properties	CCT change							
												CCDS/CIFU/Label-Change-0005344	Pharmacokinetic properties	CCT change							
												CCDS/CIFU/Label-Change-0005497	Preclinical safety data	CCT change							
												CCDS/CIFU/Label-Change-0001104	Dosage and method of administration	CCT change.				EV-PR-0022769	Gadovist, Solution for injection in pre-filled syr, 1 mmol per 1 ml	Gadobutrol	
												CCDS/CIFU/Label-Change-0001628	Indication(s)	CCT change.				EV-PR-0022771	Gadovist, Solution for injection, 1 mmol per 1 ml	Gadobutrol	4007819, Gadobutrol
												CCDS/CIFU/Label-Change-0002177	List of excipients	CCT change.							
CCDS/CIFU Event-001073	REC - 00000253		28 Oct 1999	CCT change.								CCDS/CIFU/Label-Change-0003582	Other	CCT change.							
												CCDS/CIFU/Label-Change-0005115	Pharmacodynamic properties	CCT change.							
												CCDS/CIFU/Label-Change-0005333	Pharmacokinetic properties	CCT change.							
												CCDS/CIFU/Label-Change-0006233	Warnings and precautions	CCT change.							
												CCDS/CIFU/Label-Change-0001464	Incompatibilities	CCT change				EV-PR-0021892	Gadovist, Solution for injection in pre-filled syr, 1 mmol per 1 ml	Gadobutrol	
CCDS/CIFU Event-001081	REC - 00000228		26 Apr 1999	CCT change								CCDS/CIFU/Label-Change-0002158	List of excipients	CCT change				EV-PR-0021894	Gadovist, Solution for injection, 1 mmol per 1 ml	Gadobutrol	4007819, Gadobutrol
												CCDS/CIFU/Label-Change-0003539	Other	CCT change							

BRIEF REPORT

MAYO CLINIC

Severe Acute Cardiopulmonary Failure Related to Gadobutrol Magnetic Resonance Imaging Contrast Reaction: Successful Resuscitation With Extracorporeal Membrane Oxygenation

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Abstract

Nonanaphylactic noncardiogenic pulmonary edema leading to cardiorespiratory arrest related to the magnetic resonance imaging contrast agent gadobutrol has rarely been reported in the literature. Rarer is the association of hypokalemia with acidosis. We report 2 patients who had severe pulmonary edema associated with the use of gadobutrol contrast in the absence of other inciting agents or events. These cases were unique not only for their rare and severe presentations but also because they exemplified the increasing role of extracorporeal membrane oxygenation in resuscitation. Emergency extracorporeal membrane oxygenation resuscitation can be rapidly initiated and successful in the setting of a well-organized workflow, and it is a viable alternative and helps improve patient outcome in cases refractory to conventional resuscitative measures.

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Except for nephrogenic systemic fibrosis syndrome in patients with renal failure and rare anaphylactic reactions, magnetic resonance imaging (MRI) contrast agents are considered harmless.[1] We describe 2 patients with an extremely rare adverse reaction to an MRI contrast agent and the concerted utilization of extracorporeal membrane oxygenation (ECMO) to successfully manage life-threatening refractory cardiorespiratory failure. Both cases were associated with use of the gadolinium (a paramagnetic metal in the lanthanide series) chelates available as gadobutrol.

CASE 1

In October 2014, a 63-year-old man with history of isolated dextrocardia underwent a routine annual outpatient cardiac MRI for suspected dilated nonischemic cardiomyopathy. This was a follow-up from 2 previous cardiac MRIs completed to monitor for a low ejection fraction of 42%, initially documented by cardiac imaging in December 2010. The previous cardiac MRIs were performed using gadolinium chelate–based contrast agents other than gadobutrol (ie, gadodiamide and gadoteridol [meglumine]). Other comorbidities included obstructive sleep apnea and hypertension. During the latest scan, he received 20 mL of intravenous (IV) gadobutrol contrast material (Gadavist, 1 mmol/mL; Bayer HealthCare Pharmaceuticals), and the scan was uneventfully completed without patient sedation. Ten minutes after completing the scan, the patient developed acute dyspnea and was immediately transferred to the nearby emergency department (ED) at Mayo Clinic.

On arrival at the ED, the patient was anxious, diaphoretic, and producing copious frothy white oral secretions. His respiratory rate was 30 breaths/min, and hemoglobin saturation (via pulse oximetry) was 60% while the patient was breathing ambient air. He was normoreactive, with a blood pressure of 111/83 mm Hg, and his pulse rate was

95 beats/min. An initial electrocardiogram demonstrated left bundle branch block. Oxygen supplementation was provided via a nonrebreathing mask, and he received epinephrine 0.3 mg intramuscularly, dexamethasone 10 mg IV, diphenhydramine 50 mg IV, and albuterol-ipratropium 0.3 mg/0.5 mg in an inspired aerosol to treat a suspected anaphylactic reaction. Arterial blood gas analysis showed pH 7.39; Po_2, 33 mm Hg; Pco_2, 39 mm Hg; and bicarbonate, 23 mmol/L. His blood lactate concentration was mildly elevated (3.0 mmol/L), but other laboratory values, such as hematocrit, leukocytes, platelets, coagulation profile, troponin, and creatinine, were normal. His serum tryptase level was 7.6 ng/mL (reference range, <11.5 ng/mL). The initial chest radiograph suggested pulmonary edema (Figure 1).

His condition continued to deteriorate, and he became hypotensive within 30 minutes of presentation to the ED. Emergent tracheal intubation was performed, and a right internal jugular central venous catheter was placed for norepinephrine administration. Vasopressin and epinephrine were subsequently given IV in incremental doses, for a total of 10 U and 75 µg, respectively. He also received IV methylene blue for ongoing hypotension and IV diuretics for worsening hypoxemia and pulmonary edema. He was transferred to the coronary care unit, where a repeat electrocardiogram showed dynamic T-wave changes in the lateral leads suggestive of possible coronary ischemia. He continued to be hypoxemic despite intensive ventilatory support with 100% oxygen and positive end-expiratory pressure of 18 cm H_2O. He underwent emergent coronary angiography, which demonstrated normal coronary arteries. Transesophageal echocardiography was performed in the coronary catheterization laboratory and revealed markedly reduced right and left ventricular systolic function. Repeat blood analysis 2 hours after arrival at the ED was significant for acute hypokalemia (potassium level, 2.8 mmol/L) despite metabolic acidosis with a blood pH of 7.2.

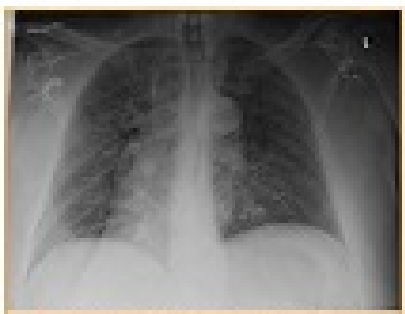

FIGURE 1. Initial chest radiograph of case 1 showing features of pulmonary edema.

In view of the tenuous hemodynamics requiring high vasopressor support and the persistent, severe hypoxemia (arterial Po_2 of 49 mm Hg), the decision was made to initiate peripheral venoarterial ECMO (VA-ECMO). Percutaneous cannulation was performed using a 17 French arterial cannula to the right femoral artery and a 23 French venous cannula to the right femoral vein. The cannulas were positioned under fluoroscopic and transesophageal echocardiographic guidance. By then, the patient developed junctional cardiac rhythm with global left ventricular hypokinesia (ejection fraction of 10%–15%). A pulmonary angiogram did not show evidence of pulmonary embolism. A temporary transcutaneous pacemaker was placed for episodes of bradycardia, and atrial septostomy was performed to prevent left ventricular overload and prevent pulmonary edema or hemorrhage. After a period of stabilization, a left femoral artery Dacron chimney graft was fashioned in the operating room for arterial inflow to maintain adequate lower-extremity perfusion. The original right venous cannula was retained.

Twenty-four hours after ECMO initiation, his hemodynamics significantly improved, and vasopressors were discontinued. Repeat bedside transesophageal echocardiography showed improved left ventricular function (ejection fraction of 40%) on day 3 of the intensive care unit stay. ECMO was discontinued, and the associated catheters were removed. The trachea was extubated the following day. The patient had no neurologic deficits, and was discharged from the intensive care unit.

CASE 2

In February 2015, a 63-year-old man with a history of compensated liver cirrhosis presented to the ED with sudden-onset respiratory distress 40 minutes after a surveillance contrast-enhanced MRI of his abdomen, performed earlier at Mayo Clinic. His medical history included hypertension, gastroesophageal reflux disease, and treated hepatitis C infection with successful seroconversion. He had no known allergies and had 2 previous MRI contrast studies with IV gadobutrol (gadoversetamide disodium and gadodiamide, not gadobutrol) without any adverse events.

During this MRI, he received 10 mL of IV gadobutrol contrast (Gadavist, 1 mmol/mL). He initially felt well after the scan but later experienced acute, severe breathlessness while driving home. Emergency medical services was contacted, and he was found in hypoxemic respiratory failure with an initial pulse oximetry of 75% while breathing ambient air. He was transported to the ED with supplemental oxygen and application of continuous positive airway pressure. On initial examination, his heart rate was 140 beats/min; respiratory rate, 40 breaths/min; and blood pressure, 133/89 mm Hg. Within 10 minutes of arrival at the ED, he developed pulseless electrical activity cardiac arrest. Chest compressions were initiated, a total of epinephrine 7 mg IV was administered, and the trachea was emergently intubated. He had return of spontaneous circulation after 12 minutes of resuscitation, but he continued to require an epinephrine infusion. Blood gas analysis showed a pH of 7.12; Po_2, 91 mm Hg; Pco_2, 36 mm Hg; and bicarbonate, 18 mmol/L. His blood lactate level was elevated (4.9 mmol/L). Except for thrombocytopenia (platelet count of 97×10^9/L), other laboratory values, such as blood hematocrit, leukocytes, prothrombin time, cardiac enzymes, serum tryptase, and renal function, were within normal limits. Chest radiograph suggested pulmonary edema (Figure 2). A bedside transthoracic echocardiogram demonstrated normal right ventricular function and a hyperdynamic but underfilled left ventricle. Repeated arterial blood gas testing 30 minutes after the return of spontaneous circulation showed worsening acidosis, with a pH of 6.87; Po_2, 48 mm Hg; Pco_2, 39 mm Hg; and bicarbonate, 14 mmol/L. His blood potassium level was 2.3 mmol/L, and his hematocrit level was 57%. Owing to persistent hemodynamic instability and clinical signs of poor tissue perfusion, ECMO was initiated. The vessels were cannulated centrally for VA-ECMO using a 22 French arterial cannula to the aorta and a 32 French venous cannula to the right atrium. The ECMO flows were established 120 minutes after initial arrest. His hospital course was complicated by severe coagulopathy requiring multiple blood product transfusions, nonoliguric renal failure, heparin-induced thrombocytopenia, and ventilator-associated pneumonia with enterobacter. After 17 days of ECMO support, he was successfully weaned from ECMO, and the vessels were decannulated. He was dismissed home 32 days after his arrest without significant neurologic deficits.

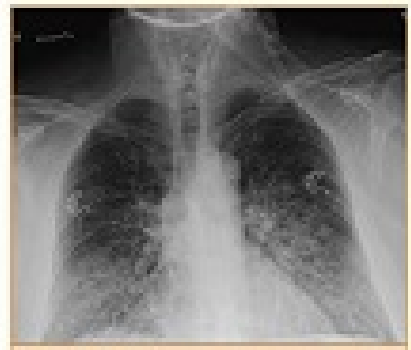

FIGURE 2. Initial chest radiograph of case 2 showing features of pulmonary edema.

DISCUSSION

These 2 cases describe a unique and rare adverse effect of gadobutrol with the successful use of VA-ECMO in the management of acute cardiorespiratory failure. To our knowledge, this is the first reported adult case series of such a clinical scenario in the United States. Gadobutrol-related pulmonary edema with severe hemodynamic compromise is rare and has been described in only 2 other cases.[2,3]

Although both of these patients had previous uneventful exposure to other gadolinium-based contrast material, the chronology of events points toward gadobutrol as the etiology of an idiosyncratic reaction. The 3 diagnostic criteria for anaphylaxis proposed in 2006 by the National Institutes of Health consensus definition were not fulfilled by either patient. Specifically, the onset of symptoms was delayed for minutes, there was no skin or mucosal involvement, and they were not allergic to MRI contrast agents in the past.[6] Neither patient had a skin rash, pruritus, or eosinophilia on presentation to support the diagnosis of allergic reaction. Additionally, serum tryptase analysis to evaluate for allergic reaction was negative. The presenting symptom of both patients was shortness of breath, with initial clinical and radiologic evidence of pulmonary edema, which rapidly progressed to cardiorespiratory arrest. We presume, in the absence of echocardiography to assess ventricular function at presentation, that cardiac failure was related to the electrolytic imbalance and acidosis in both patients and was a secondary factor, rather than the primary inciting event, for pulmonary edema.

The present cases have similar clinical features as described in the 2 previous case reports of patients who deteriorated after gadobutrol exposure, in particular hypokalemia in the presence of severe acidosis.[1,2] The pathogenesis of gadobutrol-related noncardiogenic pulmonary edema is unknown. The most commonly postulated mechanisms involve endothelial damage either due to the direct effect of the agent in the lungs or secondary to complement activation.[7,8] Gadobutrol use has been reported to result in blockade of the potassium current in an animal model and may be the reason for the observed severe hypokalemia.[7] Gadobutrol-induced pulmonary edema leading to cardiorespiratory failure was reported in 2 young patients previously. The 11-year-old girl required venovenous ECMO support, but the 37-year-old man was managed conservatively. Although conservative, supportive management was adequate for the recovery of a younger (37-year-old), healthier patient previously described, the present patients' advanced age and underlying cardiac and liver dysfunction likely aggravated the cardiorespiratory decompensation, which necessitated VA-ECMO initiation.[1]

At present, there are 9 MRI contrast agents approved for clinical use. They differ in physical properties and result in different image quality. Gadobutrol, first approved for use in 2006, provides superior delineation of small vessels and is reported to be well suited for fast imaging sequences, such as cardiac MRI.[1,9] Gadobutrol has a similar adverse effect profile as other gadolinium-based contrast agents, and severe adverse reactions are particularly rare.[9] Collectively, the reported incidence of hypersensitivity reactions due to gadolinium-related contrast is only 0.07%. In a study specifically of gadobutrol, only 2 instances (0.01%) of severe reactions (one anaphylactoid, the other severe itching and swelling of the throat) were reported among 14,299 patients.[10]

In 2014 and before the 2 cases reported herein, a thorough analysis led to the approval of gadobutrol as the gadolinium contrast of choice at Mayo Clinic. The primary impetus for this decision was patient safety. After the 2 cases of suspected gadobutrol-induced reactions described in this report, an immediate and extensive review of the cases was undertaken. The advisory group included physicians, nurses, administrators, pharmacists, physicists, purchasing/logistic personnel, and members of the advisory panel of the manufacturer. The result of this diligent inquiry determined that these were unfortunate and exceedingly rare reactions. The Contrast and Medication Committee and the Radiology Specialty Council are continuing to monitor closely for any type of gadolinium reaction. In the meantime, gadobutrol continues to be used, when indicated, as an MRI contrast agent at Mayo Clinic.

These 2 cases also highlight the effective and early use of VA-ECMO resuscitation in rapidly deteriorating patients. It allows time to achieve diagnosis and delivery of definitive therapy without compromising end-organ perfusion or function, as evident by intact neurologic function and absence of end-organ injury after the periods of tenuous oxygenation and hemodynamics.[11,12] Emergency ECMO initiation by the percutaneous or central approach can be rapidly achieved in the setting of a well-organized workflow.

CONCLUSION

Noncardiogenic pulmonary edema leading to cardiorespiratory arrest, although rare, can occur in association with gadobutrol administration. Patients and health care providers should be aware of this potentially fatal reaction. Timely use of ECMO can be lifesaving in the setting of acute, medically unresponsive severe cardiorespiratory failure.

Abbreviations and Acronyms: **ECMO** = extracorporeal membrane oxygenation; **ED** = emergency department; **IV** = intravenous; **MRI** = magnetic resonance imaging; **VA-ECMO** = venoarterial extracorporeal membrane oxygenation

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Late-onset acute respiratory distress syndrome induced by a gadolinium-based contrast agent

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ABSTRACT

Rapid decline of pulmonary function in acute respiratory distress syndrome (ARDS) can make ARDS a dangerous and potentially life threatening condition. Gadolinium based contrast agents are considered safe alternatives to iodine based contrast agents, with comparatively fewer adverse effects and a lower incidence of serious adverse events, such as dyspnea or hypotension. There are five reported cases of gadolinium induced ARDS.

A 59 year old woman with respiratory failure 30 min after gadolinium administration was diagnosed with ARDS; she was admitted to the intensive care unit. Her condition improved by artificial respiration management and adrenaline and steroids administration. She was discharged on day 13.

Considering ARDS occured 30 min after gadolinium administration and findings suggesting anaphylaxis, such as wheezing and failure in organs other than the lungs, were absent, the involvement of any immediate onset reaction was excluded; thus, a diagnosis of gadolinium induced ARDS was made.

1. Introduction

Acute respiratory distress syndrome (ARDS) is a dangerous condition that can result in death owing to rapid decline of the pulmonary function. Gadolinium is a safe alternative to iodine based contrast agents, with a lower incidence of serious adverse events such as dyspnea and hypotension [1] and comparatively fewer adverse effects [2], as noted in the study patient. There have been five previously reported cases of gadolinium induced ARDS [3–7]; however, the mechanism of onset remains unknown.

2. Case report

The patient was a 59 year old woman with a history of rheumatoid arthritis. She was administered oral methotrexate 8 mg/day weekly and bucillamine 150 mg/day. She was not allergic to drugs; she had no relevant family history. She experienced circumferential abnormal sensation in her chest that had been gradually worsening since one month. She sought medical attention on the day of admission. Symptoms associated with myelitis were suspected; contrast enhanced MRI using gadobutrol was obtained on the same day. There were no clear abnormal findings on the chest radiograph obtained just before contrast-enhanced MRI (Fig. 1). There were no problems immediately after receiving the contrast agent, and the test was completed. However, acute onset dyspnea was observed 30 min after administering the contrast agent. The SpO2 level decreased to 80%, and arterial blood gas level decreased (PaO2 = 40 mmHg) (room air). Chest auscultation revealed bilateral rhonchi, and chest radiography images showed infiltrative shadows (Fig. 1). Chest computed tomography scan also revealed bilateral infiltrative shadows; these findings suggested pulmonary edema (Fig. 1). Anaphylaxis and pulmonary edema associated with contrast enhanced MRI were suspected, and 0.3 mg adrenaline was intramuscularly injected; artificial respiration management was initiated. After intubation, breathing was characterized by oxygenation failure at an arterial partial pressure of oxygen (paO2) of 82 mmHg at 6 cm H_2O positive end expiratory pressure, with a fraction of inspired oxygen (FIO2) at 0.8. Heart function was normal according to the echocardiographs obtained subsequently. The brain natriuretic peptide (BNP) level decreased from 31.7 pg/mL before onset to 23.3 pg/mL after onset, negating the likelihood of cardiogenic pulmonary edema. No other organ failure was observed; there were no findings suggesting anaphylaxis such as rash, wheezing, or abdominal symptoms. Considering the delayed onset 30 min after gadobutrol administration, ARDS associated with anaphylactic reactions was also excluded. The possibility of other diseases such as infection causing ARDS was also excluded, leading to a diagnosis of gadobutrol-induced ARDS.

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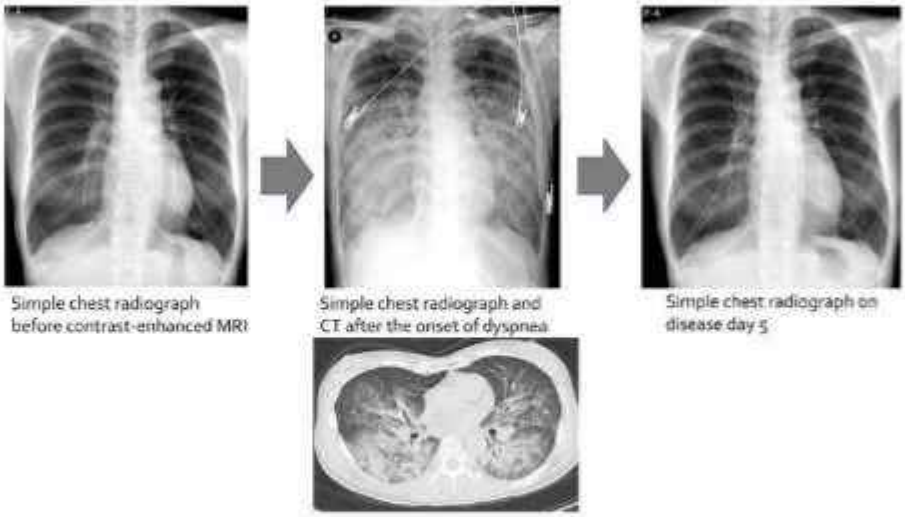

Fig. 1. Simple chest radiograph obtained just before contrast enhanced MRI. No abnormal abnormal findings in the lungs. Bilateral infiltrative shadows on a simple chest radiograph and CT after the onset of dyspnea. Simple chest radiograph on disease day 5. Improvement in infiltrative shadows was observed.

The patient was treated through positive pressure ventilation with an artificial respirator and methylprednisolone 1000 mg/day for 3 days. Chest radiography images revealed improved pulmonary edema after 5 days. Chest radiography performed on disease day 5 also revealed improved pulmonary edema (Fig. 1); thus, she was extubated on the same day. Symptoms did not worsen thereafter; she was discharged on day 13.

3. Discussion

Gadobutrol is a second-generation non-ionic macrocyclic gadolinium-based contrast agent (GBCA). It has a higher ionic concentration than other MRI contrast agents, which allows testing with smaller doses [6]; it is commonly used in contrast enhanced MRI tests. However, GBCA administered to patients with decreased renal function can trigger nephrogenic systemic fibrosis; thus, use in patients with chronic renal failure is not usually recommended [9].

Nevertheless, GBCA is associated with lower rates of adverse events than iodine-based contrast agents [2]. With the recent advances in imaging technologies, the numbers of MRI machines and images taken are increasing. The number of reports on adverse effects is also proportionately increasing [10]. Headache, dizziness, nausea and vomiting, cough, and laryngeal discomfort are the commonly reported side effects. Itchiness, rash, redness, and sneezing have also been observed [11,12].

The incidence of serious adverse events, such as dyspnea and anaphylactic hypotension, in this patient was low [1]; the incidences of adverse events after gadobutrol administration and anaphylaxis are 0.55% and 0.01%, respectively [13].

Anaphylactic reactions because of gadobutrol administration are characterized by their immediate onset; they occur in the first 5 min of administration in 82.7% cases and in the first 10 min of administration in 95.7% cases [14].

Table 1
Previously reported cases of gadolinium based contrast agent induced acute respiratory distress syndrome.

	Reference 3)	Reference 4)	Reference 5)	Reference 6)	Reference 7)
Sex	Male	Female	Female	Female	Female
Age	37 years old	46 years old	26 years old	42 years old	49 years old
Underlying diseases				Hypertension	
Tested site	Spine	Submandibular mass	Abdomen	Cervical tumor	Abdomen
Gadolinium based contrast agent	Gadobutrol	Gadobutrol	Gadobutrol	Gadobutrol	Gadobutrol
Time between administration and onset	Unknown	30 min	50 min	30 min	90 min
PaO2/FiO2	122 mmHg/1.0	139.5	63.9	n/a	48.6 mmHg/0.4
Routine chest radiography	Increased pulmonary vascular markings	Bilateral pulmonary infiltrative shadows	Bilateral pulmonary infiltrative shadows	Bilateral pulmonary infiltrative shadows	Bilateral pulmonary infiltrative shadows
Cardiac function	Good	Good	Good	Good	Good
Dyspnea	+	+	+	+	+
Lip edema	-	-	-	(-)	(-)
Wheezing	(-)	+	-	(-)	+
Loss of consciousness	-	(-)	(-)	(-)	(-)
Nausea and vomiting	(-)	(-)	-	-	(-)
Abdominal pain	(-)	(-)	(-)	(-)	(-)
Rash	(-)	(-)	(-)	(-)	(-)
Treatment	Noradrenaline, dopamine	Intramuscular adrenaline injection, steroid, steroid pulse therapy	Intramuscular adrenaline injection, steroid, norepinephrine	Steroid, steroid pulse therapy	Steroid
Outcome	Discharge without complications	Discharge without complications	Discharge without complications	Discharge without complications	Discharge without complications

ARDS is a dangerous condition characterized by a sudden drop in pulmonary function; thus, it is potentially life-threatening.

Pulmonary edema can be cardiogenic or non-cardiogenic [15]; the latter occurs as a result of increased microvascular permeability and alveolar fluid infiltration [16]. General drug-induced ARDS is caused by chemical injury of the vascular endothelium and epithelium, which triggers hypoxia and pulmonary vascular resistance by the accumulation of protein-rich substances in the alveoli [17,18]. The etiology of MRI contrast agent-induced pulmonary edema is largely unknown; however, some hypothesized mechanisms include endothelial injury triggered by the activation of the complement system and direct chemical stimulation of the alveoli [16,17].

Two reported cases of ARDS induced by CT contrast agents [19,20] are similar to this case in terms of delayed onset after the administration of the contrast agent.

To our knowledge, there are five reported cases of gadolinium-induced ARDS [3–7] (Table 1). The patient was diagnosed with ARDS following symptoms such as dyspnea that occurred 30–90 min after gadobutrol administration. The patient was treated by administration of adrenaline and steroids as well as artificial ventilation; ARDS followed good courses. However, the symptoms were delayed, occurring 30–90 min after gadobutrol administration, suggesting that gadobutrol-induced ARDS occurs by a mechanism other than an immediate reaction, exemplified by symptoms such as anaphylaxis. Delayed reactions are noted in reports on the above-mentioned iodine based contrast agents, suggesting the involvement of similar mechanisms of onset with GBCA administration. Similar to that in previously reports, our patient developed delayed-onset ARDS after gadobutrol administration and followed a good clinical course.

Previous reports have concluded that an immediate reaction was unlikely considering that ARDS development was delayed; however, the patients displayed symptoms such as cyanose, wheezing, and nausea, indicative of failure of organs other than the lungs; this suggests the involvement of anaphylaxis. However, failure of organs other than the lungs was not observed in the present case, and ARDS had a delayed onset, strongly suggesting that gadobutrol-induced ARDS onset did not involve mechanisms of an immediate reaction.

The effectiveness of subcutaneously injected gadobutrol diluted to 1:10 to test for IgE mediated GBCA allergies has been reported [21], but its actual effectiveness is questionable because the study did not define any criteria for ARDS and as mentioned previously, the onset of gadobutrol induced ARDS appears to take form of some mechanism other than an immediate reaction. This test was not performed in this patient considering the risk of fatal outcomes if it triggered ARDS recurrence.

Our results suggest that gadobutrol induced ARDS occurs through a mechanism other than that of an immediate reaction.

Declaration of competing interest

I declare on behalf of my co-authors and myself that we do not have any conflict of interest to declare.

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A rare case of acute respiratory distress syndrome caused by use of gadolinium-based magnetic resonance imaging contrast media

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Abstract

Gadolinium-based magnetic resonance imaging (MRI) contrast is generally considered to be stable and safe. Adverse reactions due to MRI contrast agents are classified into allergic-like reactions and physiological reactions. Acute respiratory distress syndrome (ARDS) caused by gadolinium-based MRI contrast is extremely rare. Due to the immediate and severe nature of ARDS, medical practitioners may seek after other aetiologies other than MRI-contrast-induced ARDS for patients' clinical manifestations such as acute-onset difficulty of breathing. It is crucial to keep in mind the possibility of ARDS after gadolinium injection, as missing the diagnosis leads to a high mortality. A clear clinical scenario of ARDS induced by gadobutrol (Gadovist, Bayer Inc., Toronto, Canada) was presented in our patient who did not develop symptoms of anaphylaxis. We successfully managed the patient with methylprednisolone and bilevel positive airway pressure ventilation and the patient was discharged in stable condition on day 6.

Introduction

Since 1988, gadopentetate dimeglumine debuted, GBCAs have been widely used and account for 30% of all magnetic resonance imaging (MRI) procedures up to date [1]. Gadolinium is composed of paramagnetic compounds that possesses a high magnetic component and is most stable with unpaired electron. Unlike iodinated contrast media, MRI contrast agents such as gadolinium have few side effects, and rarely cause anaphylactoid reactions [2]. To our best knowledge, only two cases of non-cardiogenic pulmonary oedema induced by gadolinium-based MRI contrast media have been reported [3,4]. Here, we present a Taiwanese woman who developed acute respiratory distress syndrome (ARDS) without anaphylactic symptoms after the use of gadobutrol and had a successful treatment with steroids and bilevel positive airway pressure (BiPAP) ventilation.

Case Report

A 49-year-old woman (89.9 kg, 167.1 cm, body mass index: 32.3 kg/m^2) without any past medical history, including heart failure, asthma, allergies, or immediate hypersensitivity reaction to any type of iodinated radiocontrast material, visited our hospital for a self-paid medical imaging health check-up-package which includes the MRI-upper abdomen imaging and low-dose computed tomography (LDCT) of chest. Her initial non-contrast LDCT of chest showed unremarkable finding (Fig. 1A). Two hours after LDCT, she underwent abdominal MRI after an injection of 15 mL (0.1 mL/kg body weight) of gadobutrol (Gadovist, Bayer Inc., Toronto, Canada). Ninety minutes after the injection of gadobutrol, she was found to have dyspnoea and cyanosis. Her vital signs were as follows: blood pressure 127/77 mmHg, pulse rate 100 bpm, respiratory rate 35/min, and oxygen saturation 60% by pulse oximetry.

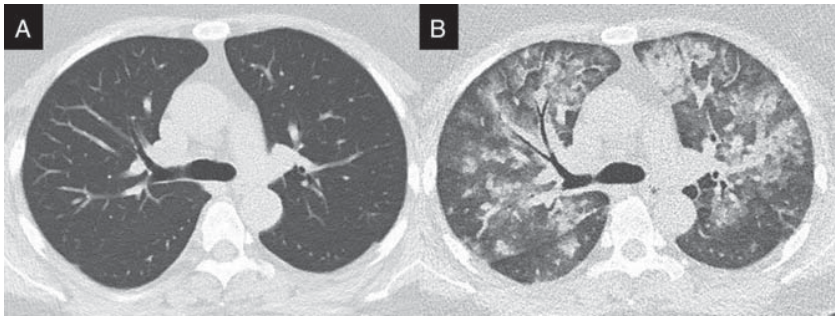

Figure 1. The chest computed tomography (CT) findings: (A) low-dose computed tomography of health check-up showed normal attenuation of bilateral lung parenchyma; (B) repeated CT scan 4 h later revealed multiple ground glass attenuation and airspace consolidation in bilateral lungs.

At emergency room, physical examinations showed diffuse wheezes and use of accessory muscles of respiration. The chest radiograph (Fig. 2A) showed bilateral alveolar infiltrates and hilar haze suggestive of acute pulmonary oedema. Laboratory tests showed a serum creatinine of 0.4 mg/dL, a D-dimer of 899 ng/mL, and a Brain Natriuretic Peptide (BNP) of 35.4 pg/mL. The repeated chest computed tomography scan showed multiple ground glass attenuation and consolidation in bilateral lungs (Fig. 1B). An echocardiography revealed no impaired left ventricular function or valvular defect. The initial arterial blood gas analysis showed a pH of 7.45, a partial pressure of carbon dioxide of 28.7 mmHg, and a partial pressure of oxygen (PaO_2) of 48.6 mmHg, which was remarkable for severe oxygenation impairment with a PaO_2/FiO_2 ratio of 121.5 (FiO_2: 40%). Under a diagnosis of MRI contrast-induced ARDS, she was transferred into intensive care unit (ICU) where BiPAP ventilation with a 15/5 cm H_2O pressure support was administered. Her hypoxaemia improved to a PaO_2 level of 85 mmHg after the use of BiPAP ventilation. In addition, she received intravenous dexamethasone 5 mg immediately at emergency room and then switched to methylprednisolone injection with a maintenance dose of 1.5 mg/kg daily. During the ICU course, the patient got improvement from respiratory distress and hypoxaemia. The repeated chest radiograph on day 3 (Fig. 2B) revealed rapid resolution of airspace infiltrates in bilateral lungs. The patient was weaned successfully from BiPAP ventilation on day 4 and she was discharged with resolution of pulmonary infiltrates (Fig. 2C) on day 6.

Discussion

Over the past two decades, since GBCA debuted, its use has been significantly increased [1]. GBCA are considered to be stable and well tolerated by patients in clinical use. Many studies have postulated transmetallation hypothesis that free gadolinium is an inhibitor of some metabolic enzymes and the release of which leads to tissue damage [5]. Awareness of GBCAs toxicity such as nephrogenic systemic fibrosis in chronic kidney disease patients has been raised. Recent studies strongly suggested gadolinium accumulation in tissue even in those with normal kidney function. However, adverse effects such as allergic reactions and non-allergic reactions due to GBCAs based contrast medium are rarely reported. Regarding GBCA-induced

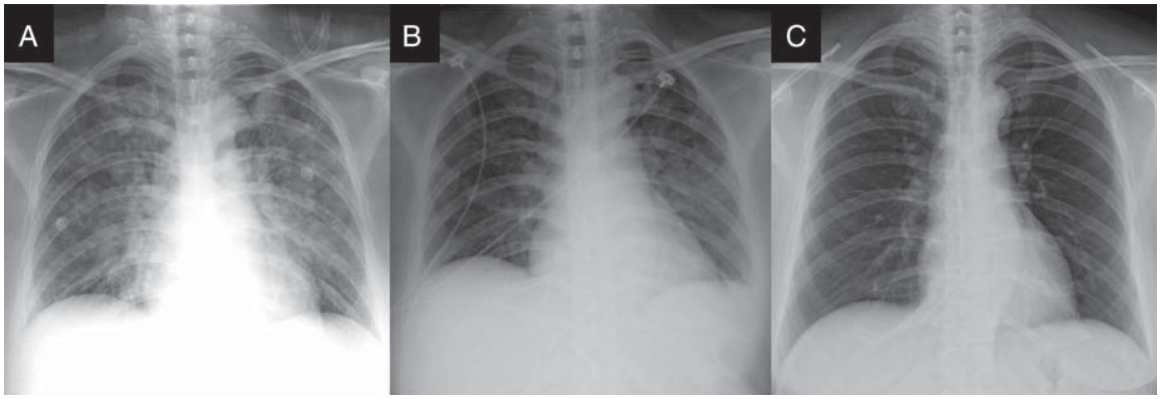

Figure 2. The serial chest radiographs: (A) breathlessness onset on day 1; (B) under bilevel positive airway pressure ventilation on day 3; (C) discharge on day 6.

hypersensitivity reactions, Galera et al. reported that GBCAs of hyperosmolarity in nature may be IgE-mediated rather than non-specific histamine release comparing to iodinated contrast media [6]. A recent meta-analysis reported immediate allergic reactions in nine studies with a total of 716,978 administrations of GBCA, the overall rates of GBCA allergic-like adverse events were 9.2 per 10,000 administrations [2].

ARDS is a sequence of an alveolar injury producing diffuse alveolar damage causing release of pro-inflammatory cytokines, which damage the capillary endothelium and alveolar epithelium. With a variety of aetiologies and its acute course of lung injury, successfully identifying and managing ARDS is critical to reduce the high mortality rate [7]. To our best knowledge, only two cases of gadolinium-induced ARDS were reported [3,4]. The two previous cases were female patients without comorbidities or allergy history [3,4], which is consistent with our patient. Park et al. [3] reported a patient who developed anaphylactic shock, angioedema of the lips, and pulmonary oedema 50 min after the injection of gadobutrol. Another case was a patient who also developed swelling of lips and uvula and pulmonary oedema 30 min after MRI-contrast administration for a submandibular mass. Due to evident allergic reactions, both cases were immediately managed with intramuscular injection of epinephrine and intravenous dexamethasone under a diagnosis of severe allergic reaction or anaphylaxis. Herein, we present a patient who developed mild ARDS according to Berlin definition [8] and was successfully treated with BiPAP ventilation and intravenous methylprednisolone. Unlike the previous cases, our patient developed dyspnoea and central cyanosis at 90 min after gadolinium injection without signs of anaphylactic reactions such as skin rash, angioedema, or hypotension. Cardiogenic pulmonary oedema was excluded in this patient because of the normal results of BNP level and echocardiography. Therefore, we hypothesized that the cause of ARDS after the administration of gadobutrol in our case is more like idiosyncratic reaction. Following methylprednisolone administration and BiPAP ventilation, the patient recovered soon as previously described cases. For medical professionals in clinical practice, we believe that awareness should be raised for patients with immediate respiratory distress without any evident skin reactions or angioedema after the administration of gadolinium-base contrast media.

According to a recent retrospective study by McDonald et al., several risk factors are identified for adverse reactions from gadolinium-based contrast agent including women, 21–50 years of age, outpatient settings, abdomen and/or pelvis MRI imaging, and MRI contrast gadobutrol or gadobenate dimeglumine [9]. Murphy et al. and Hunt et al. reported that patients who have a prior history of adverse reactions to iodinated contrast media have a higher frequency of occurrence of adverse reactions to gadolinium contrast [10,11]; however, this has not been addressed as a predictive variable in the model proposed by McDonald et al. [9]. In addition, the mechanism under the interaction between iodinated contrast media and gadolinium-based contrast is not well-established. The reason may be the rarity of the adverse reactions in patients who had undergone both imaging examinations. Nevertheless, we strongly recommend that patients with allergic-like or physiological reactions from gadolinium-based contrast should avoid both gadolinium-based contrast media and iodinated contrast media. Primary prevention such as giving patients alert card or skin testing are also suggested [12].

In conclusion, severe complications related to gadolinium-based contrast are sparse in healthy population without renal impairment for its high-safety profile. However, it is crucial to document severe allergic reaction or idiosyncratic reaction such as ARDS and provide these patients with appropriate treatment and prevention methods.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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Allergy and Airway

TOPIC: Allergy and Airway
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GADOLINIUM-INDUCED CARDIOPULMONARY ARREST IN A 57-YEAR-OLD FEMALE

CHINAZOR IWUABA ROSTISLAV GORBATOV AND LAUREN BLACKWELL

INTRODUCTION: Magnetic resonance contrast agents are used to better characterize disease processes during Magnetic Resonance Imaging (MRI). Gadolinium based contrast agents (GBCA) are widely used due to their safety profile. The incidence of adverse events after receiving GBCAs is less than 2%, most being mild and transient [1,2]. Here, we see a patient who developed cardiopulmonary arrest after GBCA administration.

CASE PRESENTATION: A 57 year old female with a past medical history of asthma, hypertension, diabetes, hyperlipidemia and mild COVID19 infection, presented to outpatient brain MRI for evaluation of new hearing loss. After receiving Gadobutrol, she developed shortness of breath, abdominal pain, and emesis. In the emergency department, the patient was hypothermic, tachypneic, and hypoxic; no urticaria or rash noted. She was placed on non-invasive ventilation and treated for presumed anaphylaxis, but remained hypoxic and in respiratory distress. Subsequent intubation (without angioedema visualized) was complicated by cardiac arrest, requiring six minutes of cardiopulmonary resuscitation. Initial imaging was significant for CT chest showing diffuse ground glass and consolidative opacities and normal CT head. Despite standard care treatment, the patient's neurological exam worsened, one week into her admission she was observed to have minimal brainstem reflexes, with head CT showing findings of anoxic brain injury, cerebral edema and possible uncal herniation. She worsened clinically and expired thirteen days after admission. Autopsy performed showed clinicopathological correlation attributing anoxic brain injury secondary to anaphylaxis.

DISCUSSION: Gadobutrol is approved for multiple indications in most ages. It was introduced in 1998, its safety profile has been studied in patients worldwide. The incidence of adverse events of GBCA has been reported to be 0.32-3.8%, commonly nausea, vomiting, urticaria and dizziness. Risk factors include patients' history of respiratory allergic disease, asthma, COPD, or prior history of reactions to iodinated contrast media [1,2]. The incidence of serious adverse drug reactions (ADR) involving the cardiopulmonary system is reported to be <0.1%; from 1998-2012 there were 614 cases of ADR of which 7.2% were fatal [3]. Our case presentation shows a severe ADR to gadolinium contrast for MRI. Though the patient's pre-existing history of asthma put her at slightly higher risk, proven safety of gadolinium contrast significantly weighs towards continued use of contrast enhanced MRI. Nevertheless, awareness and timely response to possible contrast-induced ADR is important for all clinicians.

CONCLUSIONS: GBCA are widely used agents with good safety profiles. Although severe adverse events are rare, it's important for physicians to have a high index of suspicion and use caution in patients that are identified with risk factors for adverse reactions to these agents.

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Akutes Atemnotsyndrom nach Gadoliniumanwendung

Anamnese, klinischer Befund und Diagnostik

Bei einer 20-jährigen Patientin ohne bekannte Allergien oder Vorerkrankungen und mit normalem Körpergewicht wurde eine ambulante Kernspintomographie (MRT) mit Kontrastmittel Gadobutrol (0,1 ml/kg Körpergewicht, Gadovist®) zur Abklärung einer persistierenden Gonalgie des linken Knies durchgeführt. Im Vorfeld war eine Patelladysplasie bekannt. Das einzige Dauermedikament war eine kombinierte orale hormonelle Kontrazeption. Bisher wurde der Patientin keine Art von Kontrastmittel verabreicht.

Die Patientin wurde etwa eine halbe Stunde nach der intravenösen Gabe von Gadolinium plötzlich hypoton, kollaptisch und zunehmend desorientiert. In der radiologischen Praxis erhielt sie umgehend Prednisolon und Clemastin (H1-Rezeptor-Antagonist) intravenös, mit nur geringer Besserung der Symptome. Daraufhin wurde die Patientin in unsere Notaufnahme gebracht.

Hier zeigte sich eine hypotone (RR 98/58 mm Hg) und leicht tachykarde (HF 99/min), dyspnoische Patientin. Bei schwerer Dyspnoe (SpO_2 50 %, Atemfrequenz 36/min) ohne O_2 zeigte eine arterielle Blutgasanalyse eine schwere partielle Ateminsuffizienz mit pO_2 40 mm Hg, pCO_2 30 mm Hg und SO_2 73 % bei einem pH von 7,39 und einer Temperatur von 37,1 °C. Weiterhin zeigte sich eine Hypokaliämie (2,7 mval/l) bei ansonsten unauffälligen Leber- und Nierenwerten sowie normalem Blutbild und normwertigem CRP. Bei einem Horowitz-Index von 190 bestand ein moderates ARDS (Akutes Atemnotsyndrom oder Acute respiratory distress syndrom).

Die Patientin erhielt über eine Sauerstoffmaske zunächst 12 l/min O_2 und wurde auf unsere Intensivstation aufgenommen. Dort zeigten sich radiologisch bipulmonale infiltrative Zeichnungsvermehrungen, passend zu einem ARDS (**Abb. 1**). Unter Sauerstoffzufuhr, parenteraler kristalloider Infusionstherapie und Prednisolon konnten die Vitalwerte im Verlauf stabilisiert werden. Wenige Stunden nach Aufnahme produzierte die Patientin rosafarbenen, schaumigen Auswurf und zeigte sich erneut zunehmend dyspnoisch. Eine erneute Röntgenkontrolle zeigte ein unverändertes Bild. Es erfolgte die Gabe von 40 mg Furosemid intravenös und die Sauerstoffzufuhr wurde auf 15 l/min erhöht. Darunter konnte eine Stabilisierung der Vitalwerte erreicht werden.

Um eine kardiale Genese auszuschließen erfolgte eine transthorakale Echokardiographie. Hier zeigte sich eine normale LVEF mit 60 % bei normaler Funktion aller 4 Klappen und ohne Hinweis auf eine akute Rechtsherzbelastung.

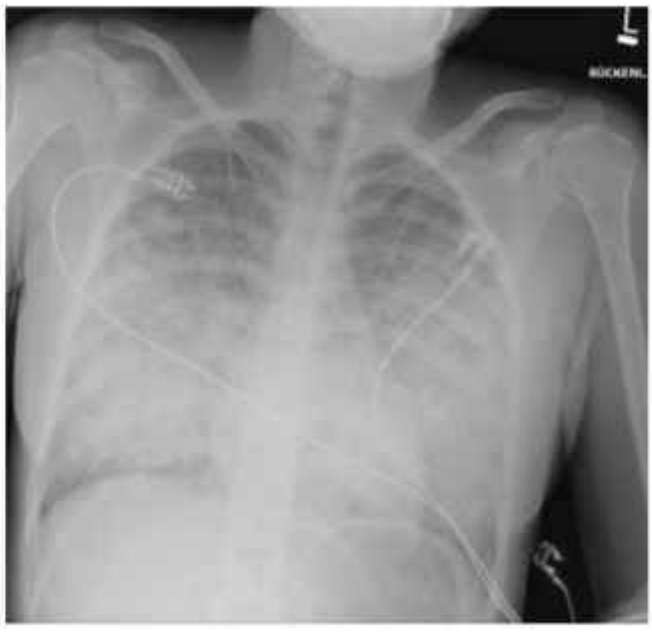

Abb. 1 ◂ Röntgenuntersuchung Thorax im Liegen bei Aufnahme. (Mit freundlicher Genehmigung © Prof. J. Wiskirchen, Klinik für Radiologie, Franziskus Hospital, Bielefeld)

Wie lautet Ihre Diagnose?

» Diagnose: Akutes Atemnotsyndrom (ARDS) nach Gadoliniumgabe

Therapie, Verlauf und Hintergrundinformationen

Unter Fortführung der medikamentösen Therapie besserte sich der Allgemeinzustand langsam, sodass die Patientin am dritten Tag von der Intensivstation auf die Normalstation verlegt werden konnte. Weitere Laborkontrollen zeigten im Verlauf eine deutliche Leukozytose (maximal 18,0 Tsd./µl) sowie einen mäßigen CRP-Anstieg (maximal 65,5 mg/l). Ergänzend erfolgte die Bestimmung von Prokalzitonin. Dieses zeigte sich mit 6,0 ng/ml deutlich erhöht. Bei klinischer und radiologischer Besserung der Luftnot sowie klinisch fehlenden Zeichen einer Sepsis wurde auf eine antibiotische Therapie verzichtet. Die Entzündungswerte zeigten sich selbstständig rückläufig, sodass wir bei der Prokalzitoninerhöhung von einer immunologisch vermittelten Reaktion ausgehen. Die Röntgenkontrolle des Thorax am dritten Tag (**Abb. 2**) zeigte eine deutliche Befundbesserung und am siebten Tag (**Abb. 3**) eine vollständige Rückbildung der Veränderungen, sodass die Patientin beschwerdefrei in die ambulante Weiterversorgung entlassen werden konnte.

In der Literatur konnten wir vier weitere ähnliche Fälle mit einem ARDS nach Gadoliniumgabe finden [2, 3, 5]. Obwohl eine Reihe von Nebenwirkungen, einschließlich nephrogener systemischer Fibrose, bekannt ist, sind schwere allergische Reaktionen mit Entwicklung eines ARDS sehr selten.

Zwischen 2004 und 2009 wurden in den USA insgesamt 40 Todesfälle im Zusammenhang mit auf Gadolinium basierenden Wirkstoffen gemeldet, von denen die meisten anaphylaktischer Genese waren [1].

In dem vorliegenden Fall fehlen klassische Zeichen einer allergischen Reaktion vom Typ I wie Juckreiz, Quaddeln oder Flush und die Latenzzeit von etwa 30 min spricht ebenfalls gegen eine IgE-vermittelte Allergie. Eine IgG-vermittelte Typ-II- oder Typ-III-Reaktion ist prinzipiell möglich, insbesondere im Hinblick auf die Entwicklung der Leukozytose, die jedoch auch kortisoninduziert sein könnte, und das erhöhte Prokalzitonin. Auf eine Bestimmung der Immunglobuline und von Komplementfaktoren wurde jedoch bewusst bei fehlender rascher Verfügbarkeit sowie fehlenden therapeutischen Konsequenzen verzichtet. Ein medikamenteninduziertes ARDS wie zum Beispiel nach Salicylsäure, trizyklischen Antidepressiva und Bleomycin ist für Gadolinium bisher nicht bekannt.

Ein ARDS wird häufiger durch eine Sepsis, Aspiration, Lungenembolie, massive Bluttransfusion, Inhalationsverletzungen oder eine akute Pankreatitis ausgelöst als infolge einer Allergie.

In diesem Zusammenhang ist zu beachten, dass als schwerwiegend eingestufte Fälle ($F_iO_2/pO_2 < 100$) eine sehr hohe Mortalität aufweisen. Der in diesem Zusammenhang einzige Fallbericht

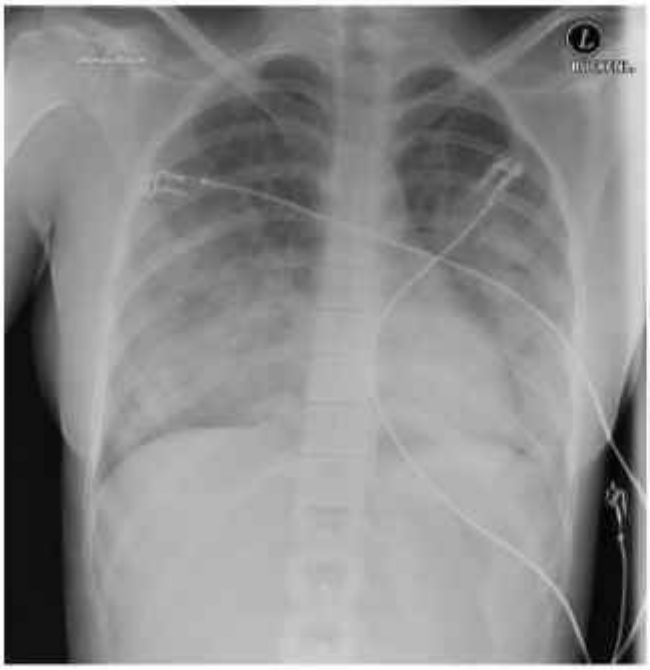

Abb. 2 ▲ Röntgenuntersuchung Thorax im Liegen an Tag 3. (Mit freundlicher Genehmigung © Prof. J. Wiskirchen, Klinik für Radiologie, Franziskus Hospital, Bielefeld)

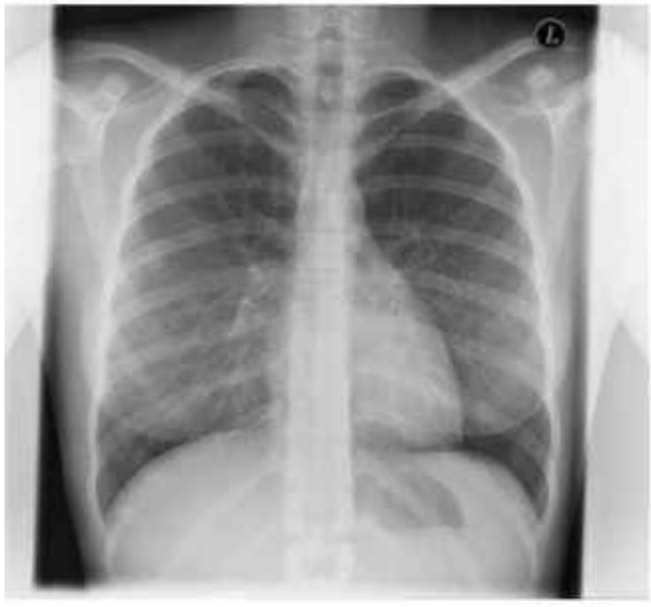

Abb. 3 ▲ Röntgenuntersuchung Thorax im Stehen an Tag 7. (Mit freundlicher Genehmigung © Prof. J. Wiskirchen, Klinik für Radiologie, Franziskus Hospital, Bielefeld)

von J.-H. Kim im Jahr 2012 konnte mithilfe einer ECMO mit einem positiven Ergebnis behandelt werden [4].

Weitere Untersuchungen zu medikamenteninduzierten bradykininvermittelten Angioödemen konnten zeigen, dass eine feste strukturierte Strategie hilfreich in der Behandlung von anaphylaktischen Reaktionen ist [6].

Fazit für die Praxis

- **Die Entwicklung eines ARDS ist eine seltene Komplikation nach Gadoliniumgabe, mit jedoch lebensbedrohlichen Folgen.**
- **Bei fehlender Besserung nach antiallergischer Therapie sind bei schwerer Dyspnoe eine rasche Diagnostik und intensivmedizinische Betreuung notwendig.**

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Einhaltung ethischer Richtlinien

Interessenkonflikt. R. Marinos und B. Husemann geben an, dass kein Interessenkonflikt besteht.

Für diesen Beitrag wurden von den Autoren keine Studien an Menschen oder Tieren durchgeführt. Für die aufgeführten Studien gelten die jeweils dort angegebenen ethischen Richtlinien. Für Bildmaterial oder anderweitige Angaben innerhalb des Manuskripts, über die Patienten zu identifizieren sind, liegt von ihnen und/oder ihren gesetzlichen Vertretern eine schriftliche Einwilligung vor.

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Fragebogen zur Covid-19 Pandemie

Bitte nehmen Sie teil!

Liebe Kolleginnen und Kollegen,
liebe/r Teilnehmer/in,

wir sind eine Forschungsgruppe in der Intensivmedizin (S. Pelz, M.Sc., Hamburg; P. Nydahl, M.Sc.N., und C. Borzikowsky, Dr. Dipl.-Psych., Universitätsklinikum Schleswig-Holstein, Campus Kiel; R. Dubb, M.A., und A. Kaltwasser, B.Sc., Akademie der Kreiskliniken Reutlingen GmbH) und laden gerne zu dieser Umfrage bezüglich der Covid-19-Pandemie ein!

In der Umfrage geht es um die Erfahrungen, die die Teilnehmer der Befragung während der Covid-19-Pandemie in ihrer praktischen Tätigkeit gemacht haben. Der Fragebogen enthält verschiedene Fragen, die u.a. Erfahrungen während der Covid-19 Pandemie erfassen. Die Bearbeitungsdauer der Umfrage beträgt etwa 10 Minuten. Für den Erfolg der Studie ist es wichtig, dass der Fragebogen vollständig ausfüllt wird und keine der Fragen auslassen werden. Alle Daten werden anonym erhoben, sie können einer Person nicht zugeordnet werden und werden streng vertraulich behandelt.

Vielen Dank für Ihre Teilnahme!

Im Namen der Forschungsgruppe
S. Pelz und A.Kaltwasser

Case Report

Yonsei Med J 56(4):1155-1157, 2015

YMJ

Acute Respiratory Distress Syndrome after the Use of Gadolinium Contrast Media

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The authors have no financial conflicts of interest.

Acute respiratory distress syndrome (ARDS) is a medical emergency that threatens life. To this day, ARDS is very rarely reported by iodine contrast media, and there is no reported case of ARDS induced by gadolinium contrast media. Here, we present a case with ARDS after the use of gadobutrol (Gadovist) as a magnetic resonance imaging (MRI) contrast medium. A 26 years old female without any medical history, including allergic diseases and without current use of drugs, visited the emergency room for abdominal pain. Her abdominopelvic computed tomography with iodine contrast media showed a right ovarian cyst and possible infective colitis. Eighty-three hours later, she underwent pelvis MRI after injection of 7.5 mL (0.1 mL/kg body weight) of gadobutrol (Gadovist) to evaluate the ovarian cyst. She soon presented respiratory difficulty, edema of the lips, nausea, and vomiting, and we could hear wheezing upon auscultation. She was treated with dexamethasone, epinephrine, and norepinephrine. Her chest X-ray showed bilateral central bat-wing consolidative appearance. Managed with mechanical ventilation, she was extubated 3 days later and discharged without complications.

Key Words: Gadolinium, gadobutrol, acute respiratory distress syndrome

INTRODUCTION

Gadolinium based contrast media have been used since 25 years ago because of their safety and low rates of side effects. Gadobutrol is a second-generation extracellular non-ionic macrocyclic gadolinium based contrast agents with high thermostability. Its gadolinium ion concentration is twice as high as other gadolinium agents, effectively resulting in high-quality images with low amount.[1]

Adverse reactions due to radiologic contrast media are not rare, but those accompanied with acute respiratory distress syndrome (ARDS) by contrast media are extremely rare. To our best knowledge, only two cases of noncardiogenic pulmonary edema induced by ionic computed tomography (CT) contrast media, such as diatrizoate and iothalamate meglumine, have so far been reported.[2,3] Also, no case of ARDS induced by magnetic resonance imaging (MRI) gadolinium contrast media has been reported yet. Here, we present a young woman who developed ARDS after the use of gadobutrol.

CASE REPORT

A 26 years old female without allergic diseases or history of taking medical image studies by using contrast media visited the emergency room for abdominal pain. Her abdominopelvic CT with contrast media showed a right ovarian cyst and possible infective colitis. Her chest X-ray and blood tests on the day of admission did not show anything significant. To evaluate the ovarian cyst, she underwent pelvis MRI after injection of 7.5 mL (0.1 mL/kg body weight) of gadobutrol (Gadovist, Bayer Inc., Toronto, Canada) 83 hours after the CT examination. Fifty minutes after the injection of gadobutrol, she presented respiratory difficulty, edema of the lips, nausea, vomiting, and wheezing upon auscultation. Her blood pressure (124/75 mm Hg) and body temperature (37.2°C) were normal, but she had tachycardia (pulse rate 109/minute) and tachypnea (respiratory rate 32/minute). Under the impression of anaphylaxis, she was given 0.5 mg of epinephrine 1:1000 intramuscularly and 5 mg of dexamethasone twice intravenously. While applying 15 L/min of oxygen via mask, arterial blood gas analysis showed pO_2 of 50.8 mm Hg and PaO_2/FiO_2 ratio of 63.5, and the chest X-ray showed bilateral central bat-wing consolidation (Fig. 1A). She rapidly developed acute respiratory failure that required mechanical ventilation (Fig. 1B). Three hours after the injection, she had hypotension (blood pressure 59/39 mm Hg) and tachycardia (pulse rate 112/min). Blood pressure did not recover after administration of 2 L of crystalloid and norepinephrine (10 mcg per minute). Six hours after the infusion, ARDS was improved on the X-ray, and transthoracic echocardiogram showed good left ventricular contractility with left ventricular ejection fraction of 60%. The ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity was 9. Norepinephrine was stopped 16 hours after intubation, and the patient was extubated 3 days later and discharged without complications (Fig. 1C). She was diagnosed with endometriotic cyst and underwent laparoscopic right ovarian cyst enucleation.

DISCUSSION

A recent study shows that gadobutrol is highly safe, with 0.55% of adverse drug reaction and less than 0.01% of serious adverse drug reaction requiring admission such as anaphylaxis.[4] Besides minor adverse effects such as feeling of warmth and taste alteration, MRI contrasts could rarely induce nephrogenic systemic fibrosis.[5] However, we could not find direct association between MRI contrasts and the lung adverse reactions, and this case has a meaningful value as the first reported case of ARDS after the use of gadobutrol. Drug-induced ARDS is a progressive clinical condition when a drug causes alveolar degradation and flooding with protein-rich material and cellular debris with subsequent increases in pulmonary vascular resistance. A complex array of endothelial injury, epithelial injury, neutrophil-mediated damage, cytokine-mediated inflammation and injury, oxidant-mediated injury, ventilator-induced lung injury, and dysregulation of coagulation and fibrinolytic pathways are all implicated in the development.[6]

Risk of adverse reactions by MR contrast media have been reported to be lower than those of CT contrast media, and cross-reactivity between MR and CT contrast media has not yet been reported. Therefore, MR contrast study has been recognized as the safe alternative for iodide contrast media allergy patients.[7] However, our patient did not show adverse reaction to CT contrast agent, suggesting the possibility of using CT contrast media as a safe alternative for MR contrast allergy patients.

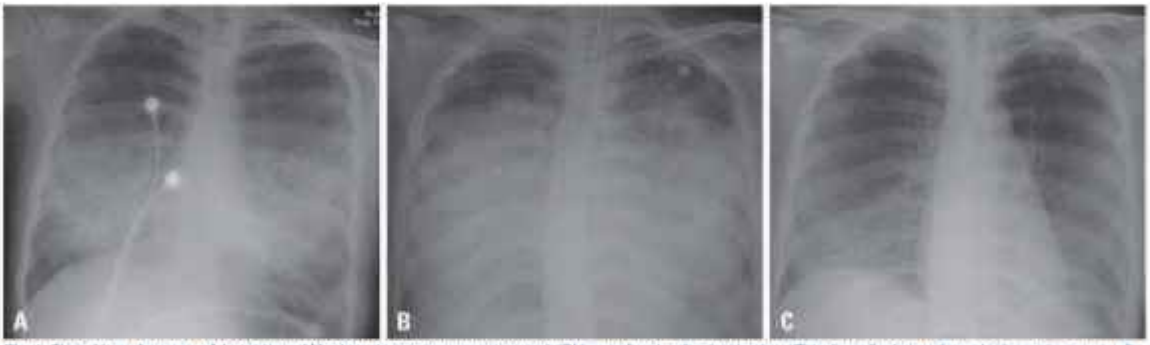

Fig. 1. Chest X-ray features of the patient: (A) when the symptoms presented, (B) immediately after intubation, (C) before discharge from the intensive care unit.

We diagnosed our patient with ARDS. She showed some clinical symptoms of anaphylaxis such as dyspnea and wheezing, but these can be explained by ARDS. Her clinical manifestations were not compatible to anaphylaxis; she developed the symptoms 50 minutes after the injection of gadobutrol, and the blood pressure was normal at the early phase of the event and then dropped 3 hours after the administration. Most cases of anaphylaxis after the use of contrast media occur within 15 minutes, and a study on gadobustrol states that 82.4% of the side effects occur within 5 minutes after the injection and 95.7% in 10 minutes.[8] The hypotension episode was not corrected despite epinephrine and massive administration of crystalloid fluid. The clinical feature of this patient was quite similar to the previously reported anaphylactoid pulmonary edema induced by ionic iodide contrast media.[2,3] Intradermal skin test and the measurement of serum tryptase at the time of the episode might have helped the differentiation of the diagnosis, but they were not done. Some investigators suggest the usefulness of 1:10 diluted intradermal skin test for IgE mediated gadolinium contrast media allergy,[9] but IgE mediated mechanism may not be critical for the development of ARDS. Furthermore, positive and negative predictive values of skin test for the diagnosis of IgE mediated gadolinium allergic diseases are yet unknown.

Besides gadobutrol, the MRI contrast media which our patient used, there are other gadolinium-based contrast media such as gadoteric acid, gadobenate, and gadodiamide. Controversy exists whether the allergic reactions of gadolinium contrast media are structure dependent. Several investigators have reported higher rate of allergic reaction by gadomenate dimeglumine than other MR contrast media,[10] suggesting the presence of specificities of gadolinium contrast media for provoking adverse reactions.

Recently, increased need for health check-ups led to increased use of MRI with contrast media as well. Doctors and other practitioners should always keep in mind the risk of ARDS after the use of gadolinium contrast media and consider the possibility of using CT contrast media as a safe alternative.

ACKNOWLEDGEMENTS

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ONLINE FIRST

Acute Respiratory Distress Syndrome
The Berlin Definition

The ARDS Definition Task Force*

The acute respiratory distress syndrome (ARDS) was defined in 1994 by the American-European Consensus Conference (AECC); since then, issues regarding the reliability and validity of this definition have emerged. Using a consensus process, a panel of experts convened in 2011 (an initiative of the European Society of Intensive Care Medicine endorsed by the American Thoracic Society and the Society of Critical Care Medicine) developed the Berlin Definition, focusing on feasibility, reliability, validity, and objective evaluation of its performance. A draft definition proposed 3 mutually exclusive categories of ARDS based on degree of hypoxemia: mild (200 mm Hg $<$ $Pao_2/Fio_2 \leq$ 300 mm Hg), moderate (100 mm Hg $<$ $Pao_2/Fio_2 \leq$ 200 mm Hg), and severe ($Pao_2/Fio_2 \leq$ 100 mm Hg) and 4 ancillary variables for severe ARDS: radiographic severity, respiratory system compliance ($\leq$40 mL/cm H_2O), positive end-expiratory pressure ($\geq$10 cm H_2O), and corrected expired volume per minute ($\geq$10 L/min). The draft Berlin Definition was empirically evaluated using patient-level meta-analysis of 4188 patients with ARDS from 4 multicenter clinical data sets and 269 patients with ARDS from 3 single-center data sets containing physiologic information. The 4 ancillary variables did not contribute to the predictive validity of severe ARDS for mortality and were removed from the definition. Using the Berlin Definition, stages of mild, moderate, and severe ARDS were associated with increased mortality (27%; 95% CI, 24%-30%; 32%; 95% CI, 29%-34%; and 45%; 95% CI, 42%-48%, respectively; $P < .001$) and increased median duration of mechanical ventilation in survivors (5 days; interquartile [IQR], 2-11; 7 days; IQR, 4-14; and 9 days; IQR, 5-17, respectively; $P < .001$). Compared with the AECC definition, the final Berlin Definition had better predictive validity for mortality, with an area under the receiver operating curve of 0.577 (95% CI, 0.561-0.593) vs 0.536 (95% CI, 0.520-0.553; $P < .001$). This updated and revised Berlin Definition for ARDS addresses a number of the limitations of the AECC definition. The approach of combining consensus discussions with empirical evaluation may serve as a model to create more accurate, evidence-based, critical illness syndrome definitions and to better inform clinical care, research, and health services planning.

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VALID AND RELIABLE DEFINITIONS are essential to conduct epidemiological studies successfully and to facilitate enrollment of a consistent patient phenotype into clinical trials.[1] Clinicians also need such definitions to implement the results of clinical trials, discuss prognosis with families, and plan resource allocation.

Following the initial description of acute respiratory distress syndrome (ARDS) by Ashbaugh et al[2] in 1967, multiple definitions were proposed and used until the 1994 publication of the American-European Consensus Conference (AECC) definition.[3] The AECC defined ARDS as the acute onset of hypoxemia (arterial partial pressure of oxygen to fraction of inspired oxygen [Pao_2/Fio_2] $\leq$ 200 mm Hg) with bilateral infiltrates on frontal chest radiograph, with no evidence of left atrial hypertension. A new overarching entity—acute lung injury (ALI)—was also described, using similar criteria but with less severe hypoxemia ($Pao_2/Fio_2 \leq$ 300 mm Hg).[3]

The AECC definition was widely adopted by clinical researchers and clinicians and has advanced the knowledge of ARDS by allowing the acquisition of clinical and epidemiological data, which in turn have led to improvements in the ability to care for patients with ARDS. However, after 18 years of applied research, a number of issues regarding various criteria of the AECC definition have emerged, including a lack of explicit criteria for defining acute, sensitivity of Pao_2/Fio_2 to different ventilator settings, poor reliability of the chest radiograph criterion, and difficulties distinguishing hydrostatic edema (TABLE 1).[4]

For editorial comment see p 2542.

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For these reasons, and because all disease definitions should be reviewed periodically, the European Society of Intensive Care Medicine convened an international expert panel to revise the ARDS definition, with endorsement from the American Thoracic Society and the Society of Critical Care Medicine. The objectives were to update the definition using new data (epidemiological, physiological, and clinical trials) to address the current limitations of the AECC definition and explore other defining variables.

Table 1. The AECC Definition[3]—Limitations and Methods to Address These in the Berlin Definition

	AECC Definition	AECC Limitations	Addressed in Berlin Definition
Timing	Acute onset	No definition of acute[4]	Acute time frame specified
ALI category	All patients with PaO_2/FIO_2 <300 mm Hg	Misinterpreted as PaO_2/FIO_2 = 201-300, leading to confusing ALI/ARDS term	3 Mutually exclusive subgroups of ARDS by severity ALI term removed
Oxygenation	PaO_2/FIO_2 ≤300 mm Hg (regardless of PEEP)	Inconsistency of PaO_2/FIO_2 ratio due to the effect of PEEP and/or FIO_2[5-7]	Minimal PEEP level added across subgroups FIO_2 effect less relevant in severe ARDS group
Chest radiograph	Bilateral infiltrates observed on frontal chest radiograph	Poor interobserver reliability of chest radiograph interpretation[8,9]	Chest radiograph criteria clarified Example radiographs created[a]
PAWP	PAWP ≤18 mm Hg when measured or no clinical evidence of left atrial hypertension	High PAWP and ARDS may coexist[10,11] Poor interobserver reliability of PAWP and clinical assesments of left atrial hypertension[12]	PAWP requirement removed Hydrostatic edema not the primary cause of respiratory failure Clinical vignettes created[a] to help exclude hydrostatic edema
Risk factor	None	Not formally included in definition[4]	Included When none identified, need to objectively rule out hydrostatic edema

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; FIO_2, fraction of inspired oxygen; PaO_2, arterial partial pressure of oxygen; PAWP, pulmonary artery wedge pressure; PEEP, positive end-expiratory pressure.
[a]Available on request.

Methods

Consensus Process. Three co-chairs were appointed by the European Society of Intensive Care Medicine, who in turn selected panelists based on their work in the area of ARDS and to ensure geographic representation from both Europe and North America. An overview of the consensus process used by the panel is outlined in the FIGURE. In revising the definition of ARDS, the panel emphasized feasibility, reliability, face validity (ie, how clinicians recognize ARDS), and predictive validity (ie, ability to predict response to therapy, outcomes, or both). In addition, the panel determined that any revision of the definition should be compatible with the AECC definition to facilitate interpretation of previous studies. After initial preparations and an in-person consensus discussion, a draft definition was proposed,[13] which underwent empirical evaluation. The definition was further refined through consensus discussion informed by these empirical data.

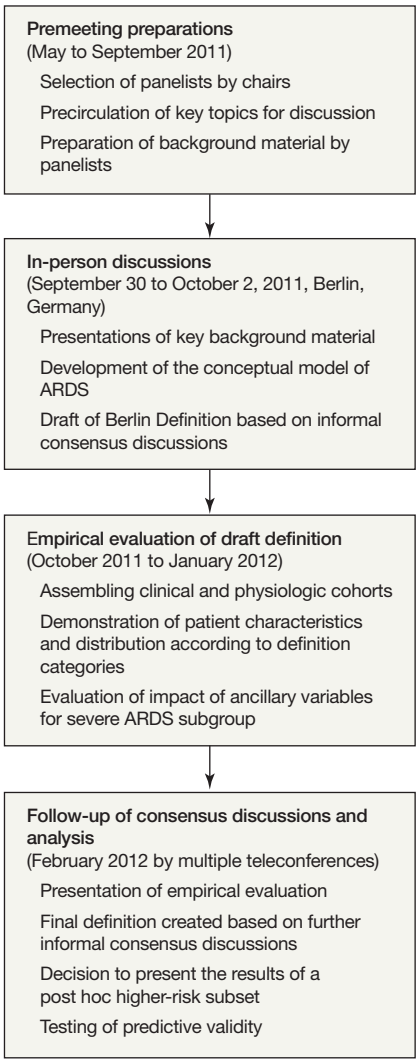
Empirical Evaluation of Draft Definition.

Cohort Assembly. Through the review of the literature presented at the consensus meeting, discussions with other experts, and review of personal files, the panel identified studies that met the following eligibility criteria: (1) large, multicenter prospective cohorts, including consecutive patients or randomized trials, or smaller, single-center prospective studies with unique radiological or physiological data that enrolled adult patients with ALI as defined by AECC; (2) studies collected granular data necessary to apply the individual criteria of both the draft Berlin Definition and the AECC definition; and (3) authors of these original studies were willing to share data and collaborate. The panel identified 7 distinct data sets (4 multicenter clinical studies for the clinical database[14-17] and 3 single-center physiological studies for the physiological database[18-20]) that met these criteria. Further details of these studies are included in the eMethods (http://www.jama.com).

Variables. Studies provided data on hospital or 90-day mortality. Ventilator-free days at 28 days after the diagnosis of ALI were calculated as a composite measure of mortality and duration of mechanical ventilation. Duration of mechanical ventilation in survivors was selected as an indirect marker of severity of lung injury because this outcome is not biased by mortality or decisions related to the withdrawal of life-sustaining treatments.[21] Progression of severity of ARDS within 7 days was assessed using the longitudinal data collected within each cohort. We distinguished patients with more extensive involvement on the frontal chest radiograph (3 or 4 quadrants) from those with the minimal criterion of "bilateral opacities" (2 quadrants).

Static compliance of the respiratory system (C_{RS}) was calculated as tidal volume (mL) divided by plateau pressure (cm H_2O) minus positive end-expiratory pressure (PEEP) (cm H_2O). The corrected expired volume per minute ($\dot{V}E_{CORR}$) was calculated as the measured minute ventilation multiplied by the arterial partial pressure of carbon dioxide ($PaCO_2$) divided by 40 mm Hg.[22] Total lung weight was estimated from quantitative computed tomography (CT) images.[23] Shunt was calculated at one site as previously reported.[24]

Figure. Outline of Consensus Process



ARDS indicates acute respiratory distress syndrome.

Analytic Framework and Statistical Methods. The analytic framework for evaluating the draft Berlin ARDS Definition was to (1) determine the distribution of patient characteristics across the defined severity categories; (2) evaluate the value of proposed ancillary variables (more severe radiographic criterion, higher PEEP levels, static respiratory compliance, and $\dot{V}E_{CORR}$) in defining the severe ARDS subgroup in the draft definition; (3) determine the predictive validity for mortality of the final Berlin Definition; and (4) compare the final Berlin Definition to the AECC definition. In addition, in a post hoc analysis, we sought thresholds for C_{RS} and $\dot{V}E_{CORR}$ that would identify a severe group of patients with ARDS who had more than 50% mortality and include more than 10% of the study population.

We did not evaluate other PaO_2/FIO_2 cutoffs or the requirement of a minimum PEEP level (5 cm H_2O) as they were selected by the panel using face validity criteria and to ensure compatibility with prior definitions. Similarly, we did not explore other variables that might improve predictive validity, such as age and severity of nonpulmonary organ failure, because they were not specific to the definition of ARDS.[25]

To compare the predictive validity of the AECC definition and the Berlin Definition, we used the area under the receiver operating curve (AUROC or C statistic) in logistic regression models of mortality with a dummy variable for the ARDS definition categories.[26] Because this technique requires independent categories to create the dummy variable and the AECC definition for ARDS is a subset of ALI, we could not compare the AECC definition as specified. Therefore, we modified the AECC definition and divided ALI into the independent categories of ALI non-ARDS (200 mm Hg $<$ $PaO_2/FIO_2 \leq$ 300 mm Hg) and ARDS alone ($PaO_2/FIO_2 \leq$ 200 mm Hg). Although the category of ALI non-ARDS is not explicitly described by the AECC, it has been used by many investigators.[27,28]

P values for categorical variables were calculated with the χ^2 test; *P* values for continuous variables were estimated with the *t* test, Mann-Whitney, analysis of variance, or Kruskal-Wallis, depending on the distribution and number of variables. The receiver operating curve statistical analyses were performed by using MedCalc for Windows version 12.1.4.0 (MedCalc Software) and other statistical tests were performed with SAS/STAT for Windows version 9.2 (SAS Institute Inc). Statistical significance was assessed at the 2-sided $P < .05$ level.

Results

Draft Consensus Definition.

The ARDS Conceptual Model. The panel agreed that ARDS is a type of acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue. The clinical hallmarks are hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space, and decreased lung compliance. The morphological hallmark of the acute phase is diffuse alveolar damage (ie, edema, inflammation, hyaline membrane, or hemorrhage).[29]

Draft Definition Criteria. Following 2 days of consensus discussions, the panel proposed a draft definition with 3 mutually exclusive severity categories (mild, moderate, and severe) of ARDS. A set of ancillary variables was proposed to further characterize severe ARDS and these were explicitly specified for further empirical evaluation.[13]

Timing. Most patients with ARDS are identified within 72 hours of recognition of the underlying risk factor, with nearly all patients with ARDS identified within 7 days.[30] Accordingly, for a patient to be defined as having ARDS, the onset must be within 1 week of a known clinical insult or new or worsening respiratory symptoms.

Chest Imaging. The panel retained bilateral opacities consistent with pulmonary edema on the chest radiograph as defining criteria for ARDS, but also explicitly recognized that these findings could be demonstrated on CT scan instead of chest radiograph. More extensive opacities (ie, 3 or 4 quadrants on chest radiograph) were proposed as part of the severe ARDS category and identified for further evaluation.

Origin of Edema. Given the declining use of pulmonary artery catheters and because hydrostatic edema in the form of cardiac failure or fluid overload may coexist with ARDS,[10,11] the pulmonary artery wedge pressure criterion was removed from the defini-

Table 2. Exploration of Proposed Variables to Define Severe ARDS[a]

Severe ARDS Definition	Mild		Moderate		Severe	
	No. (%) of Patients	% Mortality (95% CI)	No. (%) of Patients	% Mortality (95% CI)	No. (%) of Patients	% Mortality (95% CI)
Consensus panel draft						
Pa_{O_2}/F_{IO_2} ≤100 mm Hg + chest radiograph of 3 or 4 quadrants + PEEP ≥10 cm H_2O + (C_{RS} ≤40 mL/cm H_2O or $\dot{V}E_{CORR}$ ≥10 L/min)	220 (22)	27 (24-30)	2344 (64)	35 (33-36)	507 (14)	45 (40-49)[b]
Consensus panel final						
Pa_{O_2}/F_{IO_2} ≤100 mm Hg	220 (22)	27 (24-30)	1820 (50)	32 (29-34)	1031 (28)	45 (42-48)[b,c]

Abbreviations: ARDS, acute respiratory distress syndrome; C_{RS}, compliance of the respiratory system; F_{IO_2}, fraction of inspired oxygen; Pa_{O_2}, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; $\dot{V}E_{CORR}$, corrected expired volume per minute.

[a] The moderate group includes patients with Pa_{O_2}/F_{IO_2} ≤200 mm Hg and patients with Pa_{O_2}/F_{IO_2} ≤100 mm Hg who do not meet the additional criteria for severe ARDS in the draft definition. All patients are receiving at least 5 cm H_2O PEEP and have bilateral infiltrates on chest radiograph.

[b] $P < .001$ comparing mortality across stages of ARDS (mild, moderate, severe) for draft and final definitions.

[c] $P = .97$ comparing mortality in consensus draft severe ARDS to consensus final severe ARDS definitions.

tion. Patients may qualify as having ARDS as long as they have respiratory failure not fully explained by cardiac failure or fluid overload as judged by the treating physician using all available data. If no ARDS risk factor (eTable 1) is apparent, some objective evaluation (eg, with echocardiography) is required to help eliminate the possibility of hydrostatic edema.

Oxygenation. The term *acute lung injury* as defined by the AECC was removed, due to the perception that clinicians were misusing this term to refer to a subset of patients with less severe hypoxemia rather than its intended use as an inclusive term for all patients with the syndrome. Positive end-expiratory pressure can markedly affect Pa_{O_2}/F_{IO_2}[5,6]; therefore, a minimum level of PEEP (5 cm H_2O), which can be delivered noninvasively in mild ARDS, was included in the draft definition of ARDS. A minimum PEEP level of 10 cm H_2O was proposed and empirically evaluated for the severe ARDS category.

Additional Physiologic Measurements. Compliance of the respiratory system largely reflects the degree of lung volume loss.[2] Increased dead space is common in patients with ARDS and is associated with increased mortality.[24] However, because the measurement of dead space is challenging, the panel chose minute ventilation standardized at a Pa_{CO_2} of 40 mm Hg ($\dot{V}E_{CORR}$ = minute ventilation × Pa_{CO_2}/40) as a surrogate.[22] The draft definition of severe ARDS included the requirement of either a low respiratory system compliance (<40 mL/cm H_2O), a high $\dot{V}E_{CORR}$ (>10 L/min), or both. These variables were identified for further study during the evaluation phase.

The panel considered a number of additional measures to improve specificity and face validity for the increased pulmonary vascular permeability and loss of aerated lung tissue that are the hallmarks of ARDS, including CT scanning, and inflammatory or genetic markers (eTable 2). The most common reasons for exclusion of these measures were lack of routine availability, lack of safety of the measure in critically ill patients, or a lack of demonstrated sensitivity, specificity, or both for use as a defining characteristic for ARDS.

Empirical Evaluation of the Draft Definition.

Patients. A total of 4188 patients in the clinical database had sufficient data to classify as having ARDS by the AECC definition. Of these patients, 518 (12%) could not be classified by the draft Berlin Definition because PEEP was missing or was less than 5 cm H_2O. Patients who could not be classified by the draft Berlin Definition had a mortality rate of 35% (95% CI, 31%-39%), a median (interquartile range [IQR]) of 19 (1-25) ventilator-free days, and a median (IQR) duration of mechanical ventilation in survivors of 4 (2-8) days. These patients were excluded from analyses of the draft Berlin Definition and comparisons between the AECC definition and the draft Berlin Definition.

Compared with patients from the population-based cohorts, patients from clinical trials and the academic centers cohorts were younger, had more severe hypoxemia, and had more opacities on chest radiographs. The cohort of patients from the clinical trials had the lowest mortality, likely reflecting the inclusion and exclusion criteria of the trials.[31] The cohort of patients from academic centers had the highest mortality and the lowest percentage of trauma patients, reflecting the referral population (eTable 3).

There were 269 patients in the physiological database with sufficient data to classify ARDS by the AECC definition, although the numbers of patients in each cohort were small. Patients in the Turin cohort had worse Pa_{O_2}/F_{IO_2} ratios and had higher mortality than the other studies (eTable 4).

Evaluation of Ancillary Variables. The draft Berlin Definition for severe ARDS that included a Pa_{O_2}/F_{IO_2} of 100 mm Hg or less, chest radiograph with 3 or 4 quadrants with opacities, PEEP of at least 10 cm H_2O, and either a C_{RS} of 40 mL/cm H_2O or less or a $\dot{V}E_{CORR}$ of at least 10 L/min identified a smaller set of patients with identical mortality to the simpler severe ARDS category of Pa_{O_2}/F_{IO_2} of 100 mm Hg or less (**TABLE 2**). To address the possibility that the C_{RS} and $\dot{V}E_{CORR}$ thresholds might be different in patients with higher body weight, we evaluated weight-adjusted cutoffs for

these variables in one of the cohorts. There was no significant difference in the predictive validity of the weight-adjusted criteria. The consensus panel reviewed these results and considered the lack of evidence for predictive validity of these ancillary variables and their potential contribution to face validity and construct validity and decided to use the simpler definition for severe ARDS that relied on oxygenation alone.

The Berlin Definition. The final Berlin Definition of ARDS is shown in TABLE 3. Twenty-two percent (95% CI, 21%-24%) of patients met criteria for mild ARDS (which is comparable with the ALI non-ARDS category of the AECC definition; TABLE 4), 50% (95% CI, 48%-51%) of patients met criteria for moderate ARDS, and 28% (95% CI, 27%-30%) of patients met criteria for severe ARDS. Mortality increased with stages of ARDS from mild (27%; 95% CI, 24%-30%) to moderate (32%; 95% CI, 29%-34%) to severe (45%; 95% CI, 42%-48%). Median (IQR) ventilator-free days declined with stages of ARDS from mild (20 [1-25] days) to moderate (16 [0-23] days) to severe (1 [0-20] day). Median (IQR) duration of mechanical ventilation in survivors increased with stages of ARDS from mild (5 [2-11] days) to moderate (7 [4-14] days) to severe (9 [5-17] days).

Using the Berlin Definition, 29% (95% CI, 26%-32%) of patients with mild ARDS at baseline progressed to moderate ARDS and 4% (95% CI, 3%-6%) progressed to severe ARDS within 7 days; and 13% (95% CI, 11%-14%) of patients with moderate ARDS at baseline progressed to severe ARDS within 7 days. All differences between outcome variables across categories of modified AECC (ALI non-ARDS and ARDS alone) and across categories of Berlin Definition (mild, moderate, and severe) were statistically significant ($P<.001$).

Compared with the AECC definition, the final Berlin Definition had better predictive validity for mortality with an AUROC of 0.577 (95% CI, 0.561-0.593) vs 0.536 (95% CI, 0.520-0.553; $P<.001$), with the difference in AUROC of 0.041 (95% CI, 0.030-0.050). To ensure that missing PEEP data in one of the cohorts did not bias the results, the regression analysis was repeated without this cohort and yielded similar results.

The Berlin Definition performed similarly in the physiological database as in the clinical database (TABLE 5, eFigure 1, and eFigure 2). Twenty-five percent (95% CI, 20%-30%) of patients met criteria for mild ARDS, 59% (95% CI, 54%-66%) of patients met criteria for moderate ARDS, and 16% (95% CI, 11%-21%) of patients met criteria for severe ARDS. Mortality increased with stages of ARDS from mild (20%; 95% CI, 11%-31%) to moderate (41%; 95% CI, 33%-49%) to severe (52%; 95% CI, 36%-68%), with $P=.001$ for differences in mortality across stages of ARDS. Median (IQR) ventilator-free days declined with stages of ARDS from mild

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	Pao_2/Fio_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
[a] Chest radiograph or computed tomography scan.
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pao_2/Fio_2 × (barometric pressure/760)].
[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Table 4. Predictive Validity of ARDS Definitions in the Clinical Database

	Modified AECC Definition[a]		Berlin Definition ARDS[a]		
	ALI Non-ARDS	ARDS	Mild	Moderate	Severe
No. (%) [95% CI] of patients	1001 (24) [23-25]	3187 (76) [75-77]	819 (22) [21-24]	1820 (50) [48-51]	1031 (28) [27-30]
Progression in 7 d from mild, No. (%) [95% CI]		336 (34) [31-37]		234 (29) [26-32]	33 (4) [3-6]
Progression in 7 d from moderate, No. (%) [95% CI]					230 (13) [11-14]
Mortality, No. (%) [95% CI][b]	263 (26) [23-29]	1173 (37) [35-38]	220 (27) [24-30]	575 (32) [29-34]	461 (45) [42-48]
Ventilator-free days, median (IQR)[b]	20 (2-25)	12 (0-22)	20 (1-25)	16 (0-23)	1 (0-20)
Duration of mechanical ventilation in survivors, median (IQR), d[b]	5 (2-10)	7 (4-14)	5 (2-11)	7 (4-14)	9 (5-17)

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; Fio_2, fraction of inspired oxygen; IQR, interquartile range; Pao_2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure.
[a] The definitions are the following for ALI non-ARDS (200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg, regardless of PEEP), ARDS (Pao_2/Fio_2 ≤ 200 mm Hg, regardless of PEEP), mild Berlin Definition (200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP ≥5 cm H_2O), moderate Berlin Definition (100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O), and severe Berlin Definition (Pao_2/Fio_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O).
[b] Comparisons of mortality, ventilator-free days, and duration of mechanical ventilation in survivors across categories of modified AECC (ALI non-ARDS and ARDS) and across categories of Berlin Definition (mild, moderate, and severe) are all statistically significant ($P<.001$).

Table 5. Predictive Validity of ARDS Definitions in the Physiologic Database

	Modified AECC Definition[a]		Berlin Definition ARDS[a]		
	ALI Non-ARDS	ARDS	Mild	Moderate	Severe
No. (%) [95% CI] of patients	66 (25) [19-30]	203 (75) [70-80]	66 (25) [20-30]	161 (59) [54-66]	42 (16) [11-21]
Mortality, No. (%) [95% CI][b]	13 (20) [11-31]	84 (43) [36-50]	13 (20) [11-31]	62 (41) [33-49]	22 (52) [36-68]
Ventilator-free days					
Median (IQR)	8.5 (0-23.5)	0 (0-16.0)	8.5 (0-23.5)	0 (0-16.5)	0 (0-6.5)
Missing, No.	10	26	10	25	1
Duration of mechanical ventilation in survivors, median (IQR), d	6.0 (3.3-20.8)	13.0 (5.0-25.5)	6.0 (3.3-20.8)	12.0 (5.0-19.3)	19.0 (9.0-48.0)
Lung weight, mg[c]					
Mean (SD)	1371 (360.4)	1602 (508.1)	1371 (360.4)	1556 (469.7)	1828 (630.2)
Missing, No.	16	48	16	32	16
Shunt, mean (SD), %[c,d]	21 (21)	32 (13)	21 (12)	29 (11)	40 (16)

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; F_{IO_2}, fraction of inspired oxygen; IQR, interquartile range; Pa_{O_2}, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure.

[a] The definitions are the following for ALI non-ARDS (200 mm Hg $<$ $Pa_{O_2}/F_{IO_2} \leq$ 300 mm Hg, regardless of PEEP), ARDS ($Pa_{O_2}/F_{IO_2} \leq$ 200 mm Hg, regardless of PEEP), mild Berlin Definition (200 mm Hg $<$ $Pa_{O_2}/F_{IO_2} \leq$ 300 mm Hg with PEEP $\geq$5 cm H_2O), moderate Berlin Definition (100 mm Hg $<$ $Pa_{O_2}/F_{IO_2} \leq$ 200 mm Hg with PEEP $\geq$5 cm H_2O), and severe Berlin Definition ($Pa_{O_2}/F_{IO_2} \leq$ 100 mm Hg with PEEP $\geq$5 cm H_2O).

[b] Eight patients are missing in the moderate Berlin Definition ARDS group. $P = .001$ for difference in mortality across Berlin stages of ARDS.

[c] Comparisons of lung weight and shunt across categories of modified AECC (ALI non-ARDS and ARDS) and across categories of Berlin Definition (mild, moderate, and severe) are statistically significant ($P < .001$).

[d] Only available at 1 site.

(8.5 [0-23.5] days) to moderate (0 [0-16.5] days) to severe (0 [0-6.5] days), with $P = .003$ for differences in ventilator-free days across stages of ARDS. Median (IQR) duration of mechanical ventilation in survivors increased with stages of ARDS from mild (6.0 [3.3-20.8] days) to moderate (12.0 [5.0-19.3] days) to severe (19.0 [9.0-48.0] days), with $P = .045$ for differences in duration of mechanical ventilation in survivors across stages of ARDS.

Using the Berlin Definition, stages of mild, moderate, and severe ARDS had increased mean lung weight by CT scan (1371 mg; 95% CI, 1268-1473; 1556 mg; 95% CI, 1474-1638; and 1828 mg; 95% CI, 1573-2082; respectively) and increased mean shunt (21%; 95% CI, 16%-26%; 29%; 95% CI, 26%-32%; and 40%; 95% CI, 31%-48%; respectively). Comparisons of lung weight and shunt (from the single site providing these data) across categories of modified AECC (ALI non-ARDS and ARDS alone) and across categories of Berlin Definition (mild, moderate, and severe) were statistically significant ($P < .001$) (Table 5, eFigure 3, and eFigure 4).

In a post hoc analysis, combining a Pa_{O_2}/F_{IO_2} of 100 mm Hg or less with either a C_{rs} of 20 mL/cm H_2O or less or a $\dot{V}E_{CORR}$ of at least 13 L/min identified a higher-risk subgroup among patients with severe ARDS that included 15% of the entire ARDS population and had a mortality of 52% (95% CI, 48%-56%). Patients with severe ARDS who did not meet the higher-risk subset criteria included 13% of the entire ARDS population and had a mortality rate of 37% (95% CI, 33%-41%). The difference between the mortality of patients with higher-risk severe ARDS and patients with severe ARDS who did not meet these criteria was statistically significant ($P < .001$).

Comment

Developing and disseminating formal definitions for clinical syndromes in critically ill patients are essential for research and clinical practice. Although previous proposals have relied solely on the consensus process, this is to our knowledge the first attempt in critical care to link an international consensus panel endorsed by professional societies with an empirical evaluation.

The draft Berlin Definition classified patients with ARDS into 3 independent categories but relied on ancillary variables (severity of chest radiograph, PEEP $\geq$10 cm H_2O, C_{RS} $\leq$40 mL/cm H_2O, and $\dot{V}E_{CORR}$ $\geq$10 L/min) in addition to oxygenation to define the severe ARDS group. When the ancillary variables selected by the panel were subjected to evaluation, these parameters did not identify a group of patients with higher mortality and were excluded from the final Berlin Definition after further consensus discussion. Without this evaluation, a needlessly complex ARDS definition would have been proposed. However, static respiratory system compliance and an understanding of minute ventilation are important variables for clinicians to consider in managing patients with ARDS, even though those variables were not included as part of the definition.[32]

The Berlin Definition addresses some of the limitations of the AECC definition, including clarification of the exclusion of hydrostatic edema and adding minimum ventilator settings, and provides slight improvement in predictive validity. Our study presents data on the outcomes of patients with ARDS defined according to the Berlin Definition in a large heterogeneous cohort of patients including patients managed with modern approaches to lung protective ventilation. Estimates of the prevalence and clinical outcomes of mild, moderate, and severe ARDS can be assessed from this database for research and health services planning.

Acute respiratory distress syndrome is a heterogeneous syndrome with com-

plex pathology and mechanisms. The proposed definition does not resolve this problem. Investigators may choose to design future trials using 1 or more of the ARDS subgroups as a base study population, which may be further refined using criteria specific to the putative mechanism of action of the intervention (eg, IL-6 levels for an anti–IL-6 trial or more stringent hypoxemia criteria for a study on extracorporeal membrane oxygenation). Furthermore, some variables that were excluded from the Berlin Definition because of current feasibility and lack of data on operational characteristics may become more useful in the future. We anticipate that clinical research using our model of definition development will be used to revise the definition in the future.

There are limitations to our approach. First, although the Berlin Definition had statistically significantly superior predictive validity for mortality compared with the modified AECC definition, the magnitude of this difference and the absolute values of the AUROC are small and would be clinically unimportant if the Berlin Definition was designed as a clinical prediction tool. However, predictive validity for outcome is only one criterion for evaluating a syndrome definition and the purpose of the Berlin Definition is not a prognostication tool.[33] Although the Berlin Definition was developed with a framework including these criteria, we did not empirically evaluate face validity, content validity, reliability, feasibility, or success at identifying patients for clinical trial enrollment.

Second, it is possible that our results are not generalizable because of the data sets we studied. This seems unlikely because patients from a broad range of populations, including clinical trials, academic centers, and community patients, were included in the analyses.

Third, some variables (eg, C_{RS} and PEEP) were missing in some patients in the data sets we used, either due to the mode of mechanical ventilation that precluded their measurement or the practicalities of population-based research. However, bias due to cohort selection or missing data seem unlikely because our results were robust to sensitivity analyses that excluded individual cohorts.

Fourth, it is possible that the ancillary variables did not identify a higher-risk subset because the number of quadrants on the chest radiograph cannot be assessed reliably, PEEP was not used in a predictable fashion, or C_{RS} and $\dot{V}E_{CORR}$ were not accurately measured. However, if this is true, it is likely also to be true in future studies and in clinical practice because the study database was constructed from clinical trial, academic, and community sites reflecting practice in the real world of clinical research. In addition, we evaluated PEEP and C_{RS} as used by clinicians in practice and not as a test of prespecified ventilator settings that may be better than the variables evaluated herein, but may not be practical, particularly in observational cohort studies.[5,6]

Fifth, because our study was not an exercise in developing a prognostic model for ARDS, we only considered the variables and cutoffs proposed by the consensus panel. We could not compare this definition directly to the AECC definition because the categories of that definition overlap. It is possible that the outcomes as well as the relative proportion of patients within each category of ARDS will change if the underlying epidemiology of the syndrome evolves due to changes in clinical practice or risk factors.[34] This is particularly true for the post hoc higher-risk subset reported, for which the cut points were derived from the data sets.

Conclusion

In conclusion, we developed a consensus draft definition for ARDS with an international panel using a framework that focused on feasibility, reliability, and validity. We tested that definition using empirical data on clinical outcome, radiographic findings, and physiological measures from 2 large databases constructed from 7 contributing sources to assess the predictive value of ancillary variables, refine the draft definition, and compare the predictive validity of the definition to the existing AECC definition. This approach for developing the Berlin Definition for ARDS may serve as an example for linking consensus definition activities with empirical research to better inform clinical care, research, and health services planning.

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