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COMMENTARY

Use of gadolinium contrast agents in paediatric population: Donald Rumsfeld meets Hippocrates!

[1]RUCHIR SHAH, [2]FELICE D'ARCO, [3]BRUNO SOARES, [2]JESSICA COOPER and [2]JOE BRIERLEY

[1]UCL Medical School, UCL, London, UK
[2]Great Ormond Street Hospital, London, UK
[3]John Hopkins Hospital, Baltimore, MD, USA

Address correspondence to: Mr Ruchir Shah
E-mail: *ruchir.shah.13@ucl.ac.uk*

ABSTRACT

Gadolinium is a contrast agent that is used in MRI. There is new evidence that gadolinium accumulates in a patient's body and the effects of this accumulation is unknown. This has resulted in different advice being given by European Medicine Agency and U.S. Food and Drug Administration. The European Medicine Agency recommended stopping the use of linear Gadolinium agents (requiring more proof of safety) while the Food and Drug Administration continues to permit its use (requiring more proof of harm). Gadolinium should be used if deemed clinically necessary. Children and parents should be informed of the benefits and potential harm of using gadolinium-based contrast. It is up for debate whether those imaged before with gadolinium will benefit from being informed of new evidence.

INTRODUCTION

The increasing evidence of gadolinium accumulation in human tissues following its use as an MR contrast medium is of great concern, particularly in children.[1] Previous reassurance about safety is now being challenged. With this uncertainty questions are emerging: are there safer alternatives? What provision for follow up for those exposed should now be made? Crucially, what should children and their parents now be told? Should radiologists follow the Hippocratic maxim: "first do no harm", or consider that the Rumsfeldian "unknown unknown" regarding contrast media accumulation has become the "known unknown" of its effects on the developing brain, and so amend consent procedures accordingly?

Gadolinium contrast agents

Radiologists use intravenous contrast agents to detect and characterize different types of some lesions that may be overlooked without the use of contrast.[2] MRI contrast agents are based on the rare earth metal gadolinium.[3] There are two main types of gadolinium-based contrast materials (GBCM): linear and macrocyclic agents.

GBCM have generally been considered to be safe as its chelation with other compounds prevents toxicity. However, there is a known risk of nephrogenic systemic fibrosis (NSF) in patients with Stage 3 or worse renal failure.[3,4] NSF is also more likely in patients undergoing some form of dialysis.[5] Also there is now evidence suggesting that gadolinium-based contrast accumulates in various tissues and organs in the body.[6,7] This accumulation is most noticeable in the brain and with linear agents.[8] It is important to explore this further as there is a lack of equivalent alternative agents available to clinicians to pick up similar pathology.

Evidence for accumulation

Most gadolinium contrast is excreted, but there is increasing evidence that gadolinium accumulates in the body even in the absence of renal failure.[9] However, potential clinical effects of this accumulation are unknown. Rodent[10] studies showed that linear contrast agents accumulate more than macrocyclic agents but there were no associated pathological changes to the brain parenchyma. Human studies have similarly shown increased accumulation of gadolinium in the brain particularly within the dentate nuclei.[11] Furthermore, accumulation of gadolinium has been demonstrated in other body tissues (such as the bone) although this is not clearly visible on imaging and need more invasive method of measurement.[12] In summary, we know that gadolinium is an intrinsically toxic substance and that it accumulates in the brain, but there is no evidence of tissue damage related to the accumulation.

European *vs* American Stance on GBCM

Gadolinium-based contrast comes in two types depending on how the ligand complexes form; macrocyclic and linear.[13]

Based on evidence of gadolinium accumulation in the body, the European Medicines Agency stopped recommending the use of linear gadolinium-based contrast (interestingly excluding those used for hepatic imaging, despite evidence of accumulation) for MRI imaging until further studies are carried out, whilst the U.S. Food and Drug Administration highlights that there is no evidence to suggest that gadolinium is unsafe and continues to permit its use. The Japanese authorities have issued revisions into their recommendation which take a middle ground; restricting use to clinical circumstances where contrast is necessary.[14]

The lack of clarity in information poses real dilemmas for clinicians; such as justifying whether using these contrast agents are in the best interest of the child.

ETHICS

The European Medicines Agency approach uses the *precautionary principle* in which there is a social responsibility to protect the public from exposure to harm when scientific investigation has found a plausible risk, this can only be relaxed if further scientific findings provide sound evidence of safety. This approach fits with the traditional concept of the Hippocratic Corpus from *Of the Epidemics*.

> *The physician must ….have two special objects in view with regard to disease, namely, to do good or to do no harm*

However, Food and Drug Administration interpretation would suggest this approach limits freedom to innovate and denies potential benefits. So do we need proof of harm, or proof of safety to use gadolinium? A four-principal approach, whilst limited, is ubiquitous in bioethical thinking and so:

(i) Respect for autonomy suggests allowing patients to decide for themselves. In this context, this is surely best manifested by providing full information to patients about the possible risks and benefits of the use of gadolinium.
(ii) Beneficence, and
(iii) Non-maleficence are really encapsulated in the Hippocratic maxim above. Thus, concerns for parents and their children about the new issues of the implications of previous gadolinium exposure they were assured was entirely safe, and still may prove to be so, is significant.
(iv) Justice predicates that we treat people fairly and distribute benefits, risks and costs fairly.

There are basically two groups of children and families, to consider

- Those who require MRI with contrast—for these children clear and full information about what is known about the risk and benefits of gadolinium-based MR should be provided.
- Those imaged before. Given this group were assured of the safety of the process they/their children were undergoing, now in question, the public health question is what is the benefit of notifying people when the evidence of harm is lacking?

Given no single case suggesting harm due to accumulation is highly unlikely that any lawsuits regarding what at the time was an unknown unknown could be successful if appropriate action is taken at this stage.

CONCLUSION

Recent research showing accumulation of gadolinium in brain and other human tissues raises concern about potential toxicity especially in a paediatric population.[15] We suggest the use of gadolinium only if considered strictly necessary by the clinician and radiologist. For now, only macrocyclic agents should be used (similar diagnostic accuracy but considered safer than linear). The need for gadolinium-based contrast agents in children should be considered carefully for each MRI exam. Potential risks and known benefits of gadolinium should be discussed with patients and their families.

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