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SCIENTIFIC SECTION

Report of an adverse incident in a randomized clinical trial

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This is a case report of a child who experienced a possible adverse reaction to paracetamol, in a randomized clinical trial comparing paracetamol with ibuprofen for control of orthodontic pain. Through this case report we highlight the importance of formulating a protocol for management of adverse events when designing a randomized clinical trial.

Key words: Adverse reaction, clinical trial, orthodontics, paracetamol

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Introduction

Clinical research in orthodontics has taken major steps to increase the evidence base for clinical care. The rapid increase of RCTs (randomized clinical trials) within the literature demonstrates a new culture is now establishing itself. There is a need to fully understand all aspects of conducting trials including reporting mechanisms when unexpected outcomes arise. In a well-conducted RCT it is important to record and report any adverse incidents. According to the World Medical Association Declaration of Helsinki, a statement of ethical principles for medical research in human patients, it is the duty of the researcher to provide monitoring information and especially to report any serious adverse events.[1] The Consolidated Standards of Reporting Trials (CONSORT) was introduced in 1996 to improve the quality of reporting of RCTs.[2] More recently, the CONSORT statement has been revised to include a more detailed checklist of items that should be reported. This includes 'all important adverse events or side effects in each intervention group'.[3]

Generally, adverse incidents in RCTs are poorly reported. This is highlighted in a recent systematic review by Edwards *et al.* (1999),[4] which examined RCT's, where a single dose of paracetamol or ibuprofen was compared with a placebo. Fifty-two trials were included in the review: two made no mention of adverse effects, 19 gave no method of assessment and only two described how the severity of the event was investigated. The authors suggest that the method used to record an adverse incident, affects the number of adverse incidents reported. For example, a patient diary produces a greater number of adverse event reports than verbal questioning. This should be considered when designing future RCTs. Furthermore, Papanikolaou and Ioannidis screened the Cochrane Database of Systematic Reviews for data on adverse events and found that, of the 1727 reviews examined, only 25 (18%) had 'eligible data on specific harms'. They concluded that reporting of adverse events in RCTs should be improved.[5]

Paracetamol, being inexpensive and readily available without prescription, is commonly recommended for the control of dental pain. It is also considered to be relatively safe in therapeutic doses with few drug interactions. Whilst the effects of paracetamol toxicity are well known, the incidence of adverse reactions to paracetamol, especially in children, is rare. Indeed, in a review of reported reactions to analgesics it was found that of 266 anaphylactic reactions in patients aged between 12–75 years, 20 were due to aspirin while none were caused by paracetamol.[6]

Adverse reactions to paracetamol are uncommon. Skin reactions such as urticaria and maculopapular rashes have been attributed to paracetamol hypersensitivity, as well as bronchospasm, anaphylaxis, vasculitis and Stevens Johnson syndrome.[7] There have also been reports in the literature of blood dyscrasias, such as agranulocytosis and thrombocytopaenia, but these are uncommon.[8] Most reports describe an immediate hypersensitivity-type reaction to paracetamol, with symptoms often occurring within the first hour.[9] There have been some reports of delayed reactions occurring 4–5 hours after the initial dose.[10]

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In many patients with suspected paracetamol hypersensitivity, this is not confirmed with objective testing. Indeed, only 15.5–17% of patients with suspected paracetamol hypersensitivity show a positive response when subjected to Drug Provocation Testing (DPT).[7,11]

The aim of this paper is to highlight the need to establish a protocol for the management of adverse incidents when designing an RCT.

Case report

A 12-year-old male with no relevant medical history and no history of drug allergy was recruited to a randomized controlled trial comparing paracetamol and ibuprofen for the control of orthodontic pain (Dorset Ethics Research Committee, Reference Number 04/Q2201/85). He fulfilled the inclusion criteria, being between 12 and 16 years of age, scheduled to undergo separator placement prior to fixed appliance orthodontic treatment with no history of peptic ulceration, unstable asthma, renal, hepatic or cardiac impairment and no allergy to aspirin, paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs).

He was randomly allocated to receive either paracetamol 1000 mg or ibuprofen 400 mg; both patient and operator were blind to the drug received. The patient was given two doses of the trial drug, the first at 9 a.m. and the second dose 6 hours later, at 3 p.m.. Participants in the trial were instructed that further analgesics should not be necessary, but if they were in discomfort, an additional analgesic of their choice could be taken 8 hours after the last dose of the trial drug. A space on the patient's pain diary was included to record additional analgesics taken. Participants were advised that if an adverse reaction to the trial drug occurred they should initially contact their general medical practitioner (GMP) for emergency management (to whom an information sheet had been sent) and then contact the Orthodontic Department.

On the following morning, the patient was still experiencing discomfort and self-medicated with 1000 mg of paracetamol. Several hours later he suddenly developed a rash on all parts of his body described as 'red, blotchy and itchy'. There were no other symptoms. The patient attended his GMP the following day and was prescribed a course of anti-histamines. He did not report the adverse reaction to the trial co-ordinators until 1 week after the trial drugs were given, at which time the rash had completely resolved and the patient was symptom-free.

A provisional diagnosis of drug hypersensitivity to either the trial drug or to the paracetamol was made. Since one of the trial drugs was also paracetamol we decided to break the randomization code for this patient to determine which drug the patient had received. The trial drug given was found to be paracetamol, suggesting a drug hypersensitivity reaction to paracetamol. Before a controlled Drug Provocation Test (DPT) could be organized, the patient took another dose of paracetamol on the advice of his GMP. On this occasion there was no reaction to the drug, suggesting a previous false positive result. Since the patient had already taken paracetamol without event, the DPT was deemed unnecessary.

Discussion

In this paper, we report an adverse reaction to paracetamol in a randomized clinical trial (RCT) designed to compare paracetamol and ibuprofen for control of orthodontic pain. Although hypersensitivity to paracetamol was not proven, this case highlights the need for researchers to carefully consider how to manage and report adverse incidents. In future studies, we will ensure that trial participants inform the trial coordinators immediately of any adverse incidents, so that they can receive the most appropriate management. We will also modify data collection forms to include a section for recording adverse incidents.

Misdiagnosis of hypersensitivity to paracetamol is not uncommon. A study by Messaad *et al*. found that of 898 patients referred to a drug allergy clinic, 118 had a possible reaction to paracetamol, however only 17% of these actually gave a positive result.[11] Moreover, Kvedariene *et al.* studied 84 patients with possible paracetamol hypersensitivity. They found that only 13 patients in total (15.5%) were actually found to have hypersensitivity to paracetamol on DPT.[7]

Although there have been some reports on the use of skin tests to investigate paracetamol hypersensitivity[12] this method is considered unreliable since low molecular weight proteins such as paracetamol may cause skin irritation, giving a false positive result.[13] The only definitive way to confirm a drug hypersensitivity reaction is via a DPT.[14] This involves controlled administration of the drug in a hospital setting and generally reproduces the original symptoms (sometimes milder, but never more severe), and often there is an identical or slightly delayed response.

There are several explanations as to why DPT is positive in only 15.5–17% of patients. First, because the patient is only mildly affected; secondly because DPT has induced tolerance to the drug and, thirdly, because there is a long delay between the initial adverse event

and testing resulting in desensitization.[11] A further explanation is a coincidental reaction to another substance. In the current case report, because the patient had already taken paracetamol on a subsequent occasion without reaction, the planned DPT was deemed unnecessary.

However, this case emphasizes the importance of anticipating and formulating protocols for management of adverse events in clinical trials. A well-conducted RCT should have guidelines for assessing, recording and reporting adverse drug reactions. Prior to recruitment, an accurate medical history is essential, and all patients should be given clear instructions on where to seek advice should they develop signs or symptoms. Accurate and comprehensive records of the event, including details of the severity of the reaction, should be kept and monitoring bodies informed immediately. Careful follow-up is important and the patient may be referred for specialist advice to determine if drug provocation is necessary.

Conclusions

This report highlights two key points:

- It is important to formulate a protocol for managing adverse events when designing a randomized controlled clinical trial.
- Only a small percentage (15.5–17%) of patients with suspected hypersensitivity to paracetamol are truly hypersensitive.

Authors and contributors

Rebecca McAlinden was responsible for: recruitment of the patient and follow-up of the adverse incident and drafting of the article. Pamela Ellis has overall responsibility for the clinical trial and was responsible for critical revision of the article. Jonathan Sandy was responsible for critical revision of the article. All authors have approved the final version of the manuscript.

Rebecca McAlinden is the guarantor.

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