Netherlands
The Journal of Medicine

EDITORIAL

Is this reaction caused by this drug?

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ABSTRACT

The case report on cotrimoxazole-induced pancreatitis by Versleijen *et al*. deals with the assessment of the probability that cotrimoxazole induced the acute pancreatitis: a causality assessment. In this editorial, we comment on this assessment from a clinical, pharmacological and epidemiological perspective. Moreover, the consequences of the results of the assessment are discussed.

KEYWORDS

Adverse drug reaction reporting systems, drug effects, pancreatitis, trimethoprim-sulphamethoxazole combination

The case report by Versleijen *et al.* on cotrimoxazole-induced pancreatitis deals with several important issues on drug safety and causality assessment.[1] An adverse drug reaction (ADR) is 'A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function'.[2] The wording 'a response to a drug' raises the question on causality: to what extent is the adverse event caused by the use of the drug? The answer to this question, reflecting causality assessment, requires a multidisciplinary approach from a clinical, pharmacological and epidemiological perspective.

From a clinical point of view, the temporal relationship between the use of sulphamethoxazole and the diagnosis of acute pancreatitis supports a causal relationship. The previous episode with similar epigastric pain during cotrimoxazole therapy, however, challenges causality, since recovery during ongoing use of cotrimoxazole is not very likely.

Another clinical aspect may be that a positive rechallenge strongly supports causality. However, pancreatitis may be a recurrent disease, and the recurrence of pancreatitis may be coincidentally related with the readministration of cotrimoxazole. The reason for the rechallenge, despite the strong suspicion that cotrimoxazole had caused an acute pancreatitis, raises questions. Were the physicians involved not aware of the suspicion, or was it an intended rechallenge due to the lack of an alternative antibiotic therapy?

From a pharmacological point of view, we agree with the authors that no pharmacologically plausible link exists between cotrimoxazole and pancreatitis. This implies that the pancreatitis is facilitated by traits of the patient and not by (known) pharmacological traits of the drug. Such patient-related ADRs are called type B reactions and characterised by the lack of a dose-effect relationship, very low incidence but usually severe in nature, such as anaphylactic reactions.[3] Another pharmacological issue is that trimethoprim and sulphamethoxazole both inhibit cytochrome P450 isoenzymes, such as 2C8 and 2C9.[4,5] If concomitant medication had been involved, such inhibition could have caused an increase in serum levels of co-medications that are metabolised by these enzymes.

From an epidemiological point of view, causality assessment involves the use of (pharmacovigilance) databases. In general the Netherlands Pharmacovigilance Centre Lareb

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usually uses the pharmacovigilance database of the WHO collaborating centre in Uppsala, Sweden, involving spontaneous reporting systems of more than 75 countries and with more than 3 million reports. The association between trimethoprim and/or sulphamethoxazole and pancreatitis has not been reported statistically more or less frequently than all the other associations in the entire database (reporting odds ratio 0.88 (CI 95: 0.73-1.02)). This implies that all over the world reporters of ADRs have an 'average' concern about this association as compared with their concern about all other reported associations.
Similar calculations could be made in the database with regard to the suggestion by the authors that ulphonamide hypersensitivity could be involved in the described association. Nevertheless, it should be emphasised that such calculations do not prove causality but express the concerns of reporters of ADRs. Moreover, epidemiological studies in such databases require a proper assessment of quality and completeness of the involved reports, as illustrated by a study on drug-induced acute pancreatitis in the Netherlands.[6] In this series, the time between the first intake of the suspect drug and the onset of acute pancreatitis varies between four hours (jectrolan as contrast agent during an endoscopic retrograde cholangiopancreatography (ERCP)) and two years (captopril), but the median latency time was about 15 days. This challenges the causal relationship in the described case report because of its latency period of many years.

Besides these three aspects, other sources may support causality as well. The presence of pancreatitis in the summary of product characteristics (SPC) of the involved drugs, available via www.cbg-meb.nl > medicines data bank,[7] at least implies that the causality of the association was worth mentioning. The SPCs of trimethoprim does not mention pancreatitis as ADR, in contrast to the SPCs of the combined formulation of trimethoprim with sulfamethoxazole. Moreover, previous publications on associations, as pointed out by the authors, support such an association as well.

Concluding that the reported association between cotrimoxazole and pancreatitis has sufficient body of evidence to be considered as having a 'probable' or even 'certain' causal relationship,[2] what should the consequence be for clinical practice in this patient?
First, it should not be considered a reason to withhold cotrimoxazole to a patient who needs it. Adverse effects of type B seldom occur and are unpredictable. The database of the Netherlands Pharmacovigilance Centre contains one report (out of more than 50,000 reports received between 1987 and 2005) of acute pancreatitis in association with trimethoprim and none in association with cotrimoxazole. The number of patients per year with a prescription with a combination of sulphonamide and trimethoprim between 2000 and 2004 is about 179,556.[8] Although, due to underreporting, no incidence figures should be calculated from a spontaneous reporting system, one may conclude, also based on the sparse reports in literature, that the described association is rare.
Second, the purpose of a published case report is to point to the existence of a possible association between a drug and an ADR. Its effect is not only limited to the association that has been described. It is a constant reminder to the physician that the existence of a possible ADR should be part of every differential diagnosis. Patients, physicians, dentists and pharmacists should be informed about this type B ADR, since unintended re-exposure may have a dramatic sequel. An intended re-exposure, e.g. due to the lack of alternative medications with a vital indication, should be done only under close medical supervision under well-equipped conditions.
Finally, the case report is a trigger to remind physicians treating a patient with acute pancreatitis that drugs may be involved in the aetiology and should be withhold as much as possible.

NOTE

Willem L. Diemont unexpectedly died on 25 June 2005 in Berlin while on his way to a clinical pharmacology congress in Poznan, Poland. Willem Diemont was a specialist in internal medicine and head of the unit Adverse Event Notifications of the Netherlands Pharmacovigilance Centre Lareb, which he joined in 1997.
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