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Infections can increase clozapine levels, resulting in delirium: an update.

Introduction

In 1999 the Netherlands Pharmacovigilance Centre Lareb informed the Medicines Evaluation Board on 4 cases of increased clozapine levels and delirium during an episode of infection [1]. At that time there were no similar cases published in the medical literature. Another case was received since by Lareb from the same reporter and all five cases were published in the Dutch Medical Journal (Ned Tijdschr Geneesk) in 2001 [2]. In 2002 a case report on this issue was reported by Raaska *et al.* [3] and in 2003 a similar case report was published by De Leon and Diaz [4]. No additions concerning this ADR were made to the SPCs of clozapine.

Reports

In table 1 all published cases are summarized. Cases A to E were reported to the Netherlands Pharmacovigilance Centre Lareb. Cases F and G were recently published in the medical literature [3,4].

Table 1. reports of increased clozapine levels during infections.

Patient: Sex, age	Type of infection	Average clozapine levels without infection	Daily dose of clozapine	Clozapine level during infection	Ref
A: m,63	lung infection	150-350 µg/L	350 mg	1953 µg/L	[2]
B: m,54	aspiration pneumonia	250-500 µg/L	700 mg	1580 µg/L	[2]
C: m,41	appendicitis	120-200 µg/L	600 mg	630 µg/L	[2]
D: m,45	appendicitis	200-250 µg/L	275 mg	1080 µg/L	[2]
E: m,42	wound infection	200-400 µg/L	600 mg	945 µg/L	[2]
F: f,53	bacterial pneumonia	624 µg/L (SD:± 214 µg/L)	500 mg	2074 µg/L	[3]
G: m,34	upper respiratory infection with fever	436-437 µg/L	600 mg	1245 µg/L	[4]

Other sources of information

Mechanism

In two of the mentioned publications downregulation of CYP-1A2 activity during the infection is suggested as a mechanism for the increased clozapine concentrations [2,3]. This mechanism is based on evidence that supports the link between the presence of endotoxine or proinflammatory cytokines (e.g. interleukines) and the depression of CYP-1A2 and CYP-3A4 [5-7].

Conclusion

The Netherlands Pharmacovigilance Centre Lareb previously informed the Medicines Evaluation Board in 1999 on increased clozapine levels and delirium during an episode of infection. The signal was further strengthened since by two other reported cases in the literature.

References

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