



The Curious Case of the Side Effect That Never Was?

We have all read the warnings of side effects listed in medicine pack leaflets. It is right and proper that if a volunteer feels unwell during a clinical trial of a new drug, then that fact should be recorded, but I do wonder what is the criterion for inclusion? Looking at the list of possible side effects, one comes across “may cause nausea”, “may cause headaches” and the like, side effects that some volunteers would suffer even when being treated with placebo. There is one case, however, a serious case, which I came across a few years ago that seems to have little basis in fact.

Let me be absolutely clear that I am not advocating disregarding any medical advice. In cases where there is doubt, it is always better to be cautious than cavalier, especially when you are taking medicines.

In this case, two people I know had both been admitted to hospital with a swollen mouth and severe gum pain. These are typical symptoms of a dental abscess, commonly caused by anaerobic bacteria. Both people were treated with metronidazole, but the treatment came with a dire warning of very severe side effects if the patient drank alcohol, either during the course of treatment or for several days afterwards. Death was a possibility!

A little research suggested that the metronidazole alcohol interaction is well known and it has been tried as an alternative to antabuse (disulfiram) for use as an aversion therapy in cases of alcoholism. With a little more research the story began to unravel especially when I came across a double blind clinical study of 12 patients (Visapää *et al* Ann. Pharmacother 2002; 36: 971-974) which showed no interaction at all. More interesting, however was an article in the same journal by Williams and Woodcock (Ann. Pharmacother 2000; 34: 255-257). They found 8 documented cases in the literature, most worryingly, perhaps, was one case involving a 2 year old child prescribed metronidazole together with an alcohol containing vitamin B6 syrup. In fact it was a phenobarbitol-vitamin B6 syrup, so, in common with another three of the eight cases, metronidazole was not the only drug present. The most serious case resulted in a death and “toxicity due to an ethanol-metronidazole reaction” appeared on the death certificate. This is the most interesting case of them all.

The deceased was described as a 31 year old alcohol abuser, who had been in frail health following severe chest, abdominal and head injuries resulting from a car crash. The deceased had high blood levels of acetaldehyde and ethanol and was further tested for metronidazole and disulfiram. Curiously metronidazole was found in the serum. I say “curiously” because Williams and Woodcock comment that the report (Cina *et al*, Am J Forensic Med Pathol 1996; 17:343-346) gives no details of the methodology used for the determination, and false positives from cross reacting drugs could not be excluded. In fact seven other drugs, plus vitamins and cough syrup, were found at the scene, but there was neither metronidazole nor an empty metronidazole container, and the deceased had not been prescribed metronidazole by her doctor. It was concluded (by Cina *et al*) that the deceased had taken metronidazole without her doctor's knowledge and had disposed of the empty container prior to her death. I say “concluded” but “assumed” is a better word; one common aspect of all cases examined by Williams and Woodcock is “an assumption that metronidazole’s disulfiram-like action is so generally well known and well documented that it was unnecessary to look further for an explanation”. In fact

the Cina paper itself records that previously “no fatalities have been reported due to an ethanol/metronidazole interaction”. Williams and Woodcock concluded that “the authors of all the reports presumed the metronidazole-ethanol reaction to be an established pharmacologic fact. None provided evidence that could justify their conclusions.”

One cannot blame doctors for warning patients about dangerous side effects, especially, as in the case of metronidazole, where the leaflet warns of unpleasant side effects if alcohol is consumed. Though I do note that these warnings are not as dire as the verbal warnings my friends were given. Nevertheless, surely it is not too much to ask that such warnings are based on fact and not assumption or hearsay?

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