Chapter B

Micturin and Torsades de Pointes

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RESPONDING TO SIGNALS

MICTURIN AND TORSADES DE POINTEES

Micturin® (Mictrol®, terodiline hydrochloride) was withdrawn from sale in 1991 after the discovery of an association with serious cardiac arrhythmias, most notably a rare form of ventricular tachycardia known as torsades de pointes (TP) (Wild, 1992). In most patients, TP occurs in short, self-limiting bursts that lead to temporary interruption of the circulation, causing symptoms of cerebral impairment such as dizziness, acute confusion, syncope or epileptiform fits. Occasionally, it may convert into ventricular fibrillation from which death may result. TP may co-exist with sinoatrial depression, bradycardia and heart block in some patients, which may require temporary or permanent cardiac pace-making. TP is always associated with prior QT interval lengthening in the electrocardiograph (ECG) (Ben-David and Zipes, 1993). Micturin caused prolongation of the QT interval (Stewart et al., 1992; Thomas et al., 1995; Hartigan-Go et al., 1996; Shuba et al., 1999).

Micturin had been successfully marketed for 2 years before the first report of TP. A second report was received almost exactly a year later, quickly followed by a third. A full review of the corporate safety database, and of the pre-clinical data, yielded no information that pointed to a causal relationship. Terodiline’s early use as a cardiac drug historically preceded the first published descriptions of TP (Desertenne, 1966), so it is highly likely that any cases of TP were simply not recognised, any emergent arrhythmias being attributed to the disease state. Emphasis had been put on the review because of a serious event that, according to the literature, had virtually no spontaneous incidence; it was usually associated with drugs or metabolic derangement (Stratman and

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Kennedy, 1987). (There is also a rare congenital lengthening of QT interval.) All these early cases (and most of the subsequent cases) were complicated by histories of ischaemic heart disease (IHD) and polypharmacy.

Early in 1991 the fourth report of TP was received (McCleod, Thorogood and Barnett, 1991), and, most significantly, a UK cardiac centre notified the company of an impending publication (Connolly et al., 1991) involving five cases of TP, three of which were the first reports received by the company back in 1988 and 1989. The other two were, until then, not known to the company. Six cases of a very rare disorder, apparently associated with Micturin treatment, could not be ignored. It constituted a potential safety issue and required sharing with the regulators. (Each case had, of course, been reported individually to the regulators according to prevailing serious adverse drug event (ADE) requirements. These had provoked no comments from the Medicines Control Agency (MCA) at the time.)

At this stage, it was far from certain that Micturin might have a direct causal relationship with TP:

- Experts would not entirely rule out an association of the TP with IHD, or its drug treatment, a feature in many of the reported cases.
- Despite the launch of Micturin in other countries, the United Kingdom remained alone in reporting the ADE.
- Index patients had been safely on the drug for a mean of 13 months (the longest was 2 years) before the onset of the symptoms (usually blackouts) associated with TP.

Despite these doubts, the MCA was informed of our concerns. The MCA did not share any prior concern they themselves may have had, and added no more cases to the company database. The MCA saw no need for immediate action on their part, and accepted the company plan of action that included the following:

- Full validation of each case received with on-site due diligence.
- Quantifying the level of risk through sales data.
- Reviewing prescribing experience with key prescribers for unreported cases (none was discovered).
- Re-analysis of the Prescription Event Monitoring database (PEM, Drug Safety Research Unit, University of Southampton), as the original study had not identified an arrhythmia hazard.
- Commissioning a search and case–control study of the GP research database (VAMP).
- Studying the effects of Micturin on QT interval lengthening.

By July 1991, 13 cases of TP (plus three other ventricular tachycardias) had been reported from the United Kingdom, and Micturin was reviewed at a routine meeting of the Committee on Safety of Medicines (CSM). Unexpectedly, CSM decided immediate restriction in the use of the drug was required, despite no new information from any of the research actions the company had agreed with the MCA. A ‘Dear Doctor’ letter with revised prescribing information was issued on 25 July 1991 (Asscher, 1991). Not unexpectedly, this had immediate effects. Patient and prescriber confidence was immediately lost, and prescriptions dwindled to less than 10% of peak levels in just 6 weeks. Reporting rates for not only TP but also other arrhythmias and sudden, unexplained deaths increased rapidly. Many of these reports were retrospective once the association was recognised. On Friday, 13 September 1991, the company decided, voluntarily, to withdraw the drug worldwide.

At this point of withdrawal, some 69 cases of cardiac arrhythmia and sudden, unexplained death (14 of the 69) had been reported in the United Kingdom. Only three cases had been reported from outside the United Kingdom. Reports included 13 cases of other ventricular arrhythmias and 18 brady-dysrhythmias, in addition to the TP (24 cases). Prior to this point, it was estimated that approximately 450 000 UK patients (and a further 550 000 elsewhere) had been prescribed Micturin. The risk for TP (based only on UK data) was calculated at around 1 in 18 750, but this risk increased to 1 in 6500 for any of the cited events.

Preliminary analysis results became available from the PEM and VAMP databases. In the original PEM study of 1986–87, no case of TP was discovered amongst 12 457 patients. In 1991 these data were revisited (Inman et al., 1993). As it was quite possible that cases of TP could have missed diagnosis (owing to its transient and self-limiting nature in most cases),
re-analysis included all incidents that could have been attributable to cardiac or vascular events. A comparison of the incidence of these events, and deaths, was also made with another drug (nabumetone) that had also undergone a PEM study in a similar age-range of patients. There were no pertinent differences between the two groups of patients.

In the VAMP analysis of 9716 Micturin-treated patients, one case of TP was found (Hall et al., 1993). A subsequent retrospective cohort study, taken from this group of patients, showed no differences in the overall incidence of diagnosed cardiac arrhythmias between Micturin-treated patients and controls matched for age, sex and urinary consultations. Admittedly, the power provided by the VAMP and PEM databases was not high (covering only 22 000+ patients) but, at least, they provided reassurance that there was not a larger, unrecognised problem. Most relevant cases appeared to be being reported.

Studies of QT interval lengthening on ECG have shown an undoubted correlation with Micturin treatment (Stewart et al., 1992; Thomas et al., 1995; Hartigan-Go et al., 1996; Shuba et al., 1999). As QT interval lengthening is prerequisite for TP, it must be accepted that Micturin probably played a role in the development of TP. However, it is not the purpose of this chapter to examine QT interval lengthening and its association with TP. It is important to note that since the withdrawal of Micturin, effects on QT interval have been recorded in a much wider range of drugs than the anti-arrhythmics and psychotropic drugs that dominated the early publications (Stratman and Kennedy, 1987; Yap and Camm, 2000). Perhaps the most notable of the drugs affected have been two humble, and very widely used, over-the-counter (OTC) anti-histamines, astemizole and terfenadine. (Both are available now only on prescription.) Owing to the prevalence of QT interval lengthening with so many classes of drugs now, and the ease with which the effect can be detected and measured, it is important to rule it out early in clinical development.

There are important lessons to be learned from managing the Micturin alert:

1. Never to take false comfort from the fact that a drug has had an apparently long history of safe use. The development for the earlier use will probably have pre-dated modern standards of development and adverse event reporting.

2. A change of use or indication may be exposing a new profile of the patient, more susceptible to the ADE.

3. Because an event is rare, or even previously undescribed (as TP was until 1966), do not dismiss a possible association. Thalidomide teratogenicity and practolol-associated fibrosing peritonitis caused much morbidity before anyone dared to make the association.

4. We could have reacted more to the early signals. It would have been very easy, and quick, to conduct a case–control study in patients for effects on QT interval lengthening. Unfortunately, thought processes, then, did not immediately encompass the notion that patients without TP might have QT prolongation.

In these sorts of circumstances, it is always easier to find excuses to absolve than reasons to blame.

Would earlier action have actually made any difference to the outcome? This can, perhaps, be answered by examining the reasons that lead to the withdrawal. The drug was not life saving but had potentially lethal side effects. The side effects (taken as a whole) were not all that rare, at about 1 in 6500 patients exposed (between 1 in 10 000 and 1 in 20 000 for TP alone). The risk was probably doubled in the over 75s, a large patient group for the drug (Inman et al., 1993). ECGs were not helpful, as anyone exposed to terodiline will lengthen their QT interval (but, at the time, defining when it became a pathological increase was controversial).

Terodiline had been recognised as being metabolised and excreted more slowly in the elderly during clinical development (Hallén et al., 1989), and appropriate prescribing information resulted. Whilst some patients with TP had been on inappropriately high doses for their age, most were not. Unfortunately, a serum level of terodiline had been measured in only one of the reported cases (Connolly et al., 1991). It is noteworthy that the level in this case was in fact around six times the accepted therapeutic level, and this was from, apparently, recommended dosage. Thus, there was the suspicion that QT prolongation might be related to blood levels (this was subsequently proven) (Thomas et al., 1995).
Why did many of the index patients apparently live happily with their (presumed) prolonged QT for up to 2 years, and then develop TP? Were there cofactors that combined with the QT prolongation and precipitated the TP? Hypokalaemia increases the risk of TP, also through QT lengthening. Co-prescription of other drugs also known to prolong QT interval would have been another risk factor.

Finally, it had to be accepted that there were safer, alternative treatments available. All these reasons left the company with little choice but to withdraw the drug. Some patients thought otherwise, saying they were quite prepared to risk death in order to enjoy the freedom the drug had given back to them. Most patients, and their doctors, however, had already decided the risk was not worth taking.

The irony in this recount will not have escaped the alert reader. Terodiline had owed its renaissance, as Micturin, to the discovery of side effects on the urinary bladder in cardiac patients. Cardiac side effects in urological patients proved to be its undoing.

**POSTSCRIPT**

Terodiline has since been superceded by another molecule, tolterodine. This new molecule does not prolong the QT interval. The risk was peculiar to terodiline and is not a class effect. Oxybutinin, for instance, has been shown not to affect the QT interval (Hussain et al., 1996).

**REFERENCES**


