Fluoxetine-induced phenytoin toxicity: a clinical reminder about the perils of polypharmacy

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Case report
JS is a 62-year-old patient who was admitted to a secondary care hospital from resthome care with progressive reduction in her Glasgow Coma Score (GCS). She had been commenced on fluoxetine 20mg OD (once daily) 11 days prior by the GP for low mood.

Her other medical history includes difficult-to-control epilepsy, for which she takes phenytoin 300mg OD, clobazam 20mg BD (twice daily), and levetiracetam 1g BD. Including these, she was taking 19 different medications for a number of other medical problems.

Examination was consistent with phenytoin toxicity, with a markedly elevated plasma phenytoin level of 244 umol/L (reference range 40–80 umol/L). With no other reasons for a supratherapeutic level, it was concluded that the commencement of fluoxetine was the likely cause for the grossly elevated phenytoin level.

Fluoxetine and phenytoin were withheld, and she showed slow improvement in her neurological state over the following three weeks. This correlated with a gradual decline in her plasma phenytoin levels over this period. She was subsequently discharged at her baseline, with the plan to restart phenytoin alone, once the levels were back within the normal range.

We discuss the interaction between these two commonly prescribed medications, along with wider discussion regarding polypharmacy.

Discussion
Phenytoin’s unique pharmacokinetic profile leads to problems associated with dosing and drug interactions. Following non-linear kinetics, its half-life is widely variable, dependent on dose, absorption, saturation of metabolic pathways, and enzyme induction/inhibition. Metabolism is via the liver microsomal cytochrome P450 (CYP450) enzymes. Consequently, a number of drugs interactions exist. Along with this, phenytoin is a potent CYP450 inducer, specifically CYP3A4 and CYP2C19. It is predominantly protein-bound, so when saturated, small changes in doses produce large variations in levels of the free drug (contributing to toxicity).

Fluoxetine is similar, in that it is largely protein-bound (95%), and metabolised by CYP450 enzymes (predominantly CYP2C19 and CYP2D6). The active form (norfluoxetine) has a long half-life (approximately 9 days).

The first report of an interaction between phenytoin and fluoxetine was in 1992 by Jalil, who described two patients who developed phenytoin toxicity after having had fluoxetine added. In 1997, Schmider et al further detailed this with in vitro testing of liver tissue from six healthy volunteers. This revealed the interaction was via inhibition of CYP2C9-mediated metabolism of phenytoin.

Spina and Perucca outlined the clinically relevant pharmacokinetic interactions of SSRIs, citing the aforementioned research regarding the interaction between fluoxetine and phenytoin via inhibition of CYP2C9. They also noted that the clinical consequences are compounded by the long half-life of fluoxetine.

This case also highlights the dangers of polypharmacy—something that has been previously well demonstrated in elderly
and residential care patients, where polypharmacy results in higher numbers of adverse reactions and complications.\textsuperscript{6,7}

This case demonstrates the vast potential for drug interactions, and highlights the need for consideration of drug choice, along with drug monitoring when prescribing new medications. It also serves to highlight the caution needed when prescribing in patients already on multiple medications and should serve as a clinical reminder of such.

\textbf{Competing interests:} Nil

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