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CASE REPORT

Reassessing the contraindication of zolmitriptan and serotonin reuptake inhibitors: an evidence-based pharmacotherapeutic case report

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INTRODUCTION

Zolmitriptan is a selective agonist at specific serotonin receptors, namely 5-HT_{1B} and 5-HT_{1D} receptors, which is believed to account for its antimigraine effects through vasoconstriction of extracerebral blood vessels and a reduction of neurogenic inflammation in the brain (1). This proposed mechanism of action applies to all triptan antimigraine compounds, however, they differ in some relevant pharmacokinetic properties including lipophilicity (1–3). Zolmitriptan is also an agonist at 5-HT_{1A}, a serotonin autoreceptor (see Table 1).

Paroxetine is also serotonergic, although rather non-specific. Like other selective serotonin reuptake inhibitors (SSRI), it exerts its pharmacologic effects by increasing synaptic serotonin concentrations resultant to its blockade of the presynaptic serotonin transporter (2). Use of zolmitriptan and paroxetine are contraindicated due to the theoretical risk of a serotonin syndrome (4). This syndrome is believed to be caused by overstimulation of $5HT_{1A}$ receptors (5) and is characterized by a wide range of neuromuscular and neuropsychiatric symptoms and autonomic dysfunction (3, 6). Serotonin syndrome can be severe and may even result in death (7).

As first-line treatment options, triptans and SSRIs are in common use in individuals suffering from migraines and depression, respectively. It is also common that many of these individuals suffer from both of these prevalent diseases concurrently. Numerous studies have demonstrated high rates of depression in individuals suffering from migraines and vice versa (8–10). Thus, there is significant potential to coprescribe these agents. On an individual basis, the contraindication against their concurrent use could either prevent harm, by avoiding a serotonin syndrome, or deny a potentially effective therapy.

As the contraindication between zolmitriptan and SSRIs is theoretically, not empirically, based and the opportunity to coprescribe these agents is likely to be frequent, a re-evaluation of the contraindication is justified. The following case provided this opportunity.

CASE DESCRIPTION

DB was a 50-year-old Caucasian male with a prior history of migraines and a current depressive episode of moderate severity. He had been taking paroxetine 50 mg once daily for 1 month after an initial dose of 20 mg was increased gradually over 6 weeks. Since initiating paroxetine therapy DB had begun to experience severe headaches without aura for which he was prescribed zolmitriptan 2·5 mg as needed. DB also suffered from renal insufficiency and irritable bowel syndrome. Most oral medications had not been tolerated in the past. Treatment with acetaminophen and ibuprofen had failed to achieve symptom relief. Intramuscular ketorolac gave modest symptom relief. Upon filling the zolmitriptan prescription, the possible risk of serotonin syndrome associated with concomitant use of triptans and SSRIs was noted and evaluated by the pharmacist on duty. Upon consultation with DB's family practitioner, zolmitriptan was changed to a migraine prevention regimen of gabapentin 1200 mg daily. There were no other identified patient-related contraindications to zolmitriptan

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Table 1. Pharmacokinetic profile of selected triptans (1, 3, 6, 14–17)

Agent	t_{max}(h)	Lipophilicity	Blood–brain barrier penetration	F (%)	*In vitro* receptor binding affinity (pKi in nM value)			Theoretical risk for SS with other serotonergic agents
					5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	
Rizatriptan	1–1·5	Moderate	Yes	47 (po)	7·0	7·4–8·1	7·9–8·5	MAOIs, SSRIs
Sumatriptan	0·5–5 (100 mg po)	Low	No	14 (po) 96 (sc) 16 (in)				MAOIs, SSRIs, lithium, TCAs
	0·25 (6 mg sc) 1–1·5(in)				6·3	7·3	7·7	
Zolmitriptan	2	Moderate	Yes	40 (po)	6·5	8·3	9·2	MAOIs, SSRIs, lithium, TCAs

po, oral; sc, subcutaneous; in, intranasal; t_{max}, time to reach peak plasma concentration; F, bioavailability; MAOIs, monoamine oxidase inhibitors; SSRIs, serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

therapy. After discussing the contraindication with the pharmacist, a pharmacy student (AB) in training decided to further evaluate the decision to avoid the use of zolmitriptan in DB.

CLINICAL QUESTION

In a 50-year-old man receiving the maximum recommended dose of paroxetine for depression, would adding zolmitriptan on an as-needed basis for the treatment of severe headaches result in serotonin syndrome?

LITERATURE SEARCH

A search of relevant databases yielded four pertinent references from PubMed and two from Cochrane Library. Medical subject headings used included serotonin syndrome, serotonin uptake inhibitors, serotonin agonists, paroxetine and drug synergism. Subheadings included adverse effects, pharmacokinetics, pharmacology, contraindications and toxicity. Some searches were limited to English language only. No new documents were retrieved using similar terms with Iowa Drug Information Service and International Pharmaceutical Abstracts. A search of Drug Interaction Facts yielded no new information. Some references were located using the Pubmed *related articles* function and from scanning the references in articles already retrieved. Product monographs were used for background information and to clarify the official status of the drug interaction. Three review articles and two drug disposition articles were also used for background information. Three clinical trials were retrieved and were considered the best available evidence for examining the contraindication. One case report provided information on paroxetine and another detailed adverse drug effect reports regarding triptan and SSRI use specifically.

RESULTS

A randomized, placebo-controlled, two-period crossover study was conducted by Smith *et al*. (11) to investigate the effects of fluoxetine on the pharmacokinetics, pharmacodynamics and tolerability of zolmitriptan. During each study period participants received placebo or fluoxetine 20 mg once daily for 28 days and a single dose of zolmitriptan 10 mg on day 28. Drug plasma concentrations, heart rate and blood pressure were monitored. The study authors concluded that fluoxetine did not alter the metabolism of zolmitriptan. Reported adverse events were mild and transient. The study was limited by its small sample size, with 16 participants completing the study.

Putnam *et al*. (12) completed a prospective, open-label, multicentre trial of 12 339 individuals to evaluate if there was a correlation between administration of sumatriptan injections and onset of adverse effects. Of the participants, 14·5% ($n = 1784$) used SSRIs and 3·9% ($n = 485$) used

paroxetine specifically. Patients were asked to record all concomitant drugs used for 1 year. Patients on SSRI therapy had a higher absolute frequency of adverse neurological effects compared with those without SSRI therapy [0·8 and 0·25%, respectively (statistical analysis not shown)]. Such a low frequency may be attributable to factors other than a drug–drug interaction. Fifteen of the adverse effects were deemed serious by the authors; however, they occurred greater than 24 h after receiving a sumatriptan dose and were not categorized as adverse interactions. The authors concluded that there was no evidence of interaction between sumatriptan and other drugs commonly used by migraineurs.

A double-blind, randomized, two-period crossover study of six men and six women (mean age: 28·5 years) receiving rizatriptan 10 mg following 14 days of treatment with placebo or paroxetine 20 mg was conducted by Goldberg *et al*. (13). Monitoring of adverse effects, vital signs including oral temperature, heart rate and blood pressure, and mood changes were carried out pre- and post-study. Plasma and urine samples were also analysed on day 14 to monitor rizatriptan and metabolite levels. No clinically significant effect of paroxetine was observed on rizatriptan plasma profiles and no major adverse effects were observed. The authors concluded that rizatriptan can safely be administered with SSRIs. Despite such a small enrolment, the study was well designed and participants were frequently and extensively monitored.

Joffe and Sokolov (7) reviewed all adverse drug effect reports regarding fluoxetine use submitted to Eli Lilly Canada Inc. Twenty-two reports were evaluated using their own three-point scale rating the strength of evidence for a possible drug–drug interaction between fluoxetine and sumatriptan. Four reports were deemed to have some evidence of interaction, in that symptoms of serotonin syndrome were evident but not clearly demonstrated. Two reports provided good evidence as symptoms associated with serotonin syndrome appeared with coadministration and resolved upon discontinuation of the second drug. No fatalities were reported. The authors acknowledged the limitations of these reports in that clinical details, treatment and course of events for each case were generally not provided, and that selective or under-reporting of adverse events may distort the prevalence of interaction between these agents. Also, the rating of cases was subjective, with variation in opinion between the reporters themselves. An indication of the frequency of coadministration and evidence of the type and extent of the drug–drug interactions were lacking. As a result of deficiencies in data reporting, the study provides weak evidence of serotonin syndrome with fluoxetine and sumatriptan use.

Leung and Ong (5) reported six cases of concurrent sumatriptan oral or subcutaneous therapy with various SSRIs for 3–18 months. A 46-year-old female reported concurrent use of sumatriptan weekly and paroxetine 20 mg daily for 3 months. No apparent adverse effects were associated with coadministration in any of the cases.

CONCLUSION

A literature search yielded limited evidence on the potential interaction between triptans and SSRIs. No adverse effects indicative of serotonin syndrome were noted by Smith *et al*. (11), Goldberg *et al*. (13) or Leung and Ong (5) with the use of fluoxetine and zolmitriptan, paroxetine and rizatriptan, and paroxetine and sumatriptan, respectively. Putnam *et al*. (12) and Joffe and Sokolov (7) reported potential cases of serotonin syndrome, but lack convincing evidence. Due to similarities of agents within SSRI and triptan classes, data from these studies were extrapolated to address the clinical question.

There is a general consensus among authors that the incidence of serotonin syndrome is rare among patients on these drugs. However, the pharmacokinetic differences amongst zolmitriptan, sumatriptan and rizatriptan could theoretically result in different outcomes. Zolmitriptan and sumatriptan possess similar affinity for 5-HT_{1A} receptors, which putatively mediate the serotonin syndrome (14). However, the initially prescribed agent zolmitriptan is moderately lipophilic and does penetrate the blood–brain barrier and is therefore capable of accessing central 5-HT_{1A} receptors. As there is more information and experience on concomitant sumatriptan and SSRI use and data demonstrating that sumatriptan does not penetrate the blood–brain barrier appreciably (1, 6), it may have been prudent to switch DB to sumatriptan as needed

rather than prophylactic therapy with gabapentin. The evidence suggests that adverse events associated with coadministration of sumatriptan and SSRIs are not life-threatening and uncommon. The evidence regarding zolmitriptan's contraindication with SSRIs remains inadequate for concluding either risk or safety.

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