Hemorrhages During Escitalopram–Venlafaxine–Mirtazapine Combination Treatment of Depression

Dear Editor: Selective serotonin reuptake inhibitors (SSRIs) may cause bleeding (1–3), probably by increasing platelet release of serotonin, which increases platelet aggregation. I report on a patient who experienced bleeding during treatment for depression when escitalopram, venlafaxine, and mirtazapine were combined but not when the same drugs were used alone.

Case Report
A man, aged 60 years, with major depressive disorder had been treated for 12 months with many antidepressants, both alone and in combination, with mild improvement. All SSRIs had been used alone at maximum dosage. The maximum dosages of venlafaxine alone and mirtazapine alone (which increase serotonin and norepinephrine) had also been used. The patient improved with escitalopram 20 mg daily. Two months later, because his depressive symptoms persisted, venlafaxine and mirtazapine were added to escitalopram. His mirtazapine dosage was 15 mg daily, and his venlafaxine dosage was 150 mg daily. One week later, the patient noted mild hemorrhages from his nose and rectum. These progressively worsened during the following 3 weeks, but not to the point of requiring emergency treatment. The patient then spontaneously gradually reduced the dosages of mirtazapine, venlafaxine, and escitalopram. Mirtazapine was reduced to 7.5 mg daily, venlafaxine to 100 mg daily, and escitalopram to 15 mg daily. In 1 week, the bleeding decreased. He continued weekly tapering the medications to escitalopram 5 mg daily, venlafaxine 37.5 mg daily, and mirtazapine 7.5 mg daily after 3 weeks. During tapering, the amount of nose and rectal blood loss progressively decreased; it stopped when the final dosages were reached. As well, the patient’s depression remitted. He experienced no serotonin syndrome.

This patient has also been taking omeprazole 20 mg daily for stomach ulcers he developed years ago, as well as, for some years, the antihypertensive irbesartan (an angiotensin II receptor inhibitor) 300 mg daily.

The onset of hemorrhages when mirtazapine and venlafaxine were added to escitalopram and the dosage–response relation between bleeding and dosages of these drugs suggest a causal link: Because previous treatments with escitalopram, venlafaxine, and mirtazapine, used alone, did not cause hemorrhages, it appears that this drug combination may have caused them. Escitalopram and venlafaxine (by blocking serotonin reuptake) and mirtazapine (by increasing serotonin release) may have increased serotonin to levels not reached with previous treatments, leading to hemorrhage by platelet aggregation. Its unlikely that the patient had a bleeding stomach ulcer, because fresh blood was seen from his nose and rectum; it is also unlikely that omeprazole increased blood levels of these drugs by blocking CYP2C19. Further, irbesartan does not inhibit P450 cytochromes. Escitalopram and mirtazapine have several metabolic pathways, and venlafaxine is metabolized by CYP2D6 (4). Therefore, pharmacokinetic interactions are unlikely to have caused the hemorrhages. Pharmacodynamic interactions leading to high levels of serotonin are a more likely cause. Escitalopram is a potent inhibitor of serotonin reuptake; venlafaxine less potently inhibits serotonin reuptake; and mirtazapine increases serotonin by blocking alpha-2 adrenergic heteroreceptors (5).

For treatment-resistant depression, clinicians should take care when combining several antidepressants that increase serotonin, bearing in mind that this combination may result in hemorrhages.

References

Franco Benazzi, MD
Forlì, Italy

Re: Lorazepam-Induced Prolongation of the QT Interval in a Patient With Schizoaffective Disorder and Complete AV Block

Dear Editor: Dr Ziegenbein and Dr Kropp reported the case of a woman, aged 40 years, with schizoaffective disorder and a complete AV heart block, concluding that 3 dosages of lorazepam induced QT prolongation (1). The basis of their conclusion appears inexplicable.

The only argument for lorazepam as the putative agent appears to be that its use coincided with recognition of the QT abnormality. Electrolyte status was not reported. The QT prolongation persisted for 7 days after the discontinuation of lorazepam and all other psychotropic agents and required pacemaker placement. Even with the patient’s reported liver dysfunction (extent unknown), the lorazepam should have been cleared long before 7 days, owing to its half-life of 14 hours and lack of active metabolites (2). If lorazepam was responsible, the QT prolongation should have reversed. In addition, the patient was also receiving another benzodiazepine, diazepam. If lorazepam was responsible, it would need to have a unique mechanism of action—one that is distinct from the other benzodiazepines, which is not the case (2).

The more likely cause of this patient’s QT prolongation and, hence, her need for a pacemaker was her cardiovascular disease and complete AV block at admission. The patient’s liver dysfunction and diazepam prescription may also have potentiated the effects of the prescribed 2 antipsychotics (quetiapine and pipamperone) and tricyclic antidepressant (trimipramine) (2). The authors cite a study involving 495 psychiatric patients that found antipsychotics and tricyclic antidepressants, but not...
benzodiazepines, to be associated with QT prolongation (3). It is curious then that the authors would reach the conclusion they did, because it stands in opposition to the literature.

Therefore, to suggest that lorazepam-induced QT prolongation in the face of multiple confounding factors, lack of an expected time course, no obvious mechanism of action for the effect, and literature stating otherwise seems curious. Instead, the case should serve as an example of how, in complicated presentations, the coincidental timing of the onset of events can lead to misinterpreted causal associations. Clinicians should not change their practice with respect to lorazepam because of the cited case; this could potentially limit the drug’s appropriate use.

References

David Crockford, MD, FRCPC Calgary, Alberta

Reply: Lorazepam-Induced Prolongation of the QT Interval in a Patient With Schizoaffective Disorder and Complete AV Block

Dear Editor: Thank you for the opportunity to respond to Dr Crockford’s letter. As active members of a drug safety program in psychiatry in Europe (Arzneimittelsicherheit in der Psychiatrie [AMSP]), we are always interested in discussing complex cases of pharmacotherapy. The AMSP is a drug safety program that ensures the continual assessment of severe adverse drug reactions in psychiatric inpatients under the naturalistic conditions of routine clinical treatment (1). The AMSP aims to collect information on the type and frequency of severe adverse drug reactions, to identify specific risk factors with regard to patient characteristics and such treatment-related factors as interactions caused by drug combinations or drug dosage, and to provide more information on how to adequately handle adverse drug reactions. Currently, 45 hospitals participate in the program.

Recent studies show that a high number of patients with severe cardiac drug reactions have frequent cardiac comorbidity (2). In addition, most receive drug combinations wherein drugs with similar adverse reaction profiles are often coprescribed. We agree with Dr Crockford that the case we presented and discussed is definitely complex with preexisting cardiovascular risks. However, we do not agree that lorazepam is not possibly associated with QT prolongation in that particular case, and we would like to comment on a few of Dr Crockford’s points. First, the electrolyte status revealed no abnormal findings, and the liver enzymes were moderately elevated. Second, the relevance of the half-life of lorazepam in relation to the duration of the QT prolongation is uncertain. Various undesired adverse drug reactions, for example skin reactions and blood dyscrasias, appear after single drug doses. Third, while we agree that a unique mechanism of action for lorazepam, distinct from the other benzodiazepines, seems to be unlikely, daily clinical work shows that substances with almost an identical chemical structure cause different side effects. Fourth, as Dr Crockford points out, there are multiple confounding factors; however, this does not preclude the possibility that lorazepam set off the mechanisms of the persisting QT prolongation.

Inspired by our work in the AMSP, we decided to present our provocative conclusions in this complex case. This case shows that, in patients taking drug combinations and having preexisting cardiovascular risks, physicians should be aware of possible unlikely adverse drug reactions. On our way from case reports to quality management of drug treatment, controversial discussions are important to classify severe adverse drug reactions. As well, further research is needed to elucidate the underlying physiological mechanisms. We definitely agree with Dr Crockford that clinicians should not change their practice with regard to lorazepam in general. Lorazepam is an important and useful drug in daily psychiatric clinical work. As with any drug, it can have side effects, some of which may be rare and peculiar.

References

Marc Ziegenbein, MD Stefan Kropp, MD Hanover, Germany

Lithium-Associated Anencephaly

Dear Editor: The most common congenital malformation (CMF) associated with lithium is Ebstein’s anomaly. Other reported effects on the fetus are poor respiratory effort, cyanosis, rhythm disturbances, nephrogenic diabetes insipidus, thyroid dysfunction, hypoglycemia, hyperbilirubinemia, floppy baby syndrome, and large-for-gestational-age infants (1). Neural tube defects have not been reported in humans.

Case Report
A woman, aged 21 years, with no medical or psychiatric history developed acute-onset manic illness that was initially treated with haloperidol (dosage unknown) and lasted for 3 weeks. She presented to our services with neuroleptic malignant syndrome and was treated with bromocriptine up to 15 mg daily, lorazepam up to 6 mg daily, and supportive management. She improved without any neurologic sequel and was started on lithium.

She remained euthymic on lithium 900 mg daily for 2 years (her serum levels were monitored regularly). She married during this period and had genetic counselling (wherein she was advised to practise contraception and to stop taking lithium if she planned a pregnancy). However, owing to contraceptive failure, she conceived. The patient and her husband decided to continue the pregnancy, despite repeat counselling. She stopped taking lithium before 8 completed weeks of pregnancy.

An investigation profile (specifically, HIV, Venerale Disease Research Laboratory slide test, TORCH Screen, hepatitis B antigen, hemogram, renal and liver function tests, and blood sugar level) was normal. She started taking folic acid, calcium, and iron supplements at approximately 8 weeks. Ultrasonography at 12 weeks showed a live fetus, aged 9 weeks. Ultrasonography at 20 weeks showed a live fetus, aged 16 weeks, with evidence of a supraorbital cranial bony defect (suggesting anencephaly) along with a
retroplacental hypochoic lesion, 4 cm \times 3 \text{ cm} in size (suggesting a retroplacental hematoma). Repeat ultrasonography at 23 weeks showed additional evidence of widening of the lower part of the spine. Because anencephaly was present in the fetus, the patient was advised to terminate the pregnancy medically. The patient refused and dropped out of treatment.

Discussion

Animal, but not human, studies have found lithium to be associated with increased neural tube defects manifesting as exencephaly (2). Anencephaly has been seen in only one animal study (3), whereas evidence for association with exencephaly is more robust (2). However, sonographic and pathologic evidence points to a close link between exencephaly and anencephaly, with exencephaly being seen as a stage in the development of anencephaly (4).

Our patient became pregnant while taking lithium, and the fetus developed anencephaly. The possible association of anencephaly with lithium in this patient cannot be ruled out, owing to the temporal relation of lithium use in the first 6 to 8 weeks of pregnancy (the period of embryogenesis and most vulnerable period for developing CMF), the absence of a family history of CMF, and exencephaly–anencephaly being recognized as occurring in animal studies involving lithium.

References


Sandee Grover, MD
Chandigarh, India
Nitin Gupta, MD,
Burton upon Trent, UK

Aripiprazole-Induced Seizure

Dear Editor: Antipsychotics, both typical and atypical, have been known to lower seizure threshold. Aripiprazole is a novel atypical antipsychotic that is a partial agonist at dopamine D2 and serotonin1A (5-HT1A) receptors and has antagonist activity at the 5-HT2 receptor. The risk of seizures with aripiprazole is reported to be 0.1% (1), the lowest among atypical agents. Our literature search revealed no report of seizure induction with aripiprazole.

Case Report

Mr A, aged 31 years, was brought to the emergency department after a motor vehicle accident. He had lost control of his vehicle, which landed in a ditch. He carried a diagnosis of delusional disorder and major depression; aripiprazole 15 mg daily had recently been added to sertraline 150 mg daily that he had been taking for the past 2 years. Both the patient and his family suspected that a seizure had caused the accident, since they were perplexed by the circumstances of the crash. The patient denied that he had attempted suicide.

Mr A was restarted on aripiprazole while he was in the intensive care unit. About 3 weeks later, he had a witnessed partial complex seizure on the ward. There was no evidence of any medical cause for the seizure. His laboratory tests were within normal limits, except for a serum magnesium level of 1.7 mg/dL (the lower normal being 1.8 mg/dL). He was started on levetiracetam, and his aripiprazole was later discontinued, because it was considered to be the offending agent. The patient was subsequently transferred to the rehabilitation unit, where he stayed seizure-free. He was discharged home after an adequate recovery.

Discussion

Seizure induction from antipsychotic drugs is not a new phenomenon. Several risk factors are known, including a personal or family history of epilepsy, head trauma, and comorbid use of another drug known to lower seizure threshold (2). Since experience with aripiprazole is limited at this time, the risk of lowering of seizure threshold with this drug may actually be higher than reported in the premarketing studies. Our patient possibly had 2 separate seizures, one of which was the witnessed event that occurred when the medication was reinitiated, making the likelihood high that aripiprazole was the offender.

Medical causes were ruled out, and there were no other implicated medications.

For optimum outcomes, high vigilance is needed to promptly identify the cause of seizures in patients taking psychotropic medications. The reliance of seizure secondary to aripiprazole needs further elucidation.

References


Asif R Malik, MD
Saj Ravasia, MD, CCFP, FRCPC, DABPN
Fargo, North Dakota

Prevalence of Bipolar Disorder and Major Depression Among Patients Seen in Primary and Secondary Care in Finland

Dear Editor: The underdiagnosis of bipolar disorder (BD) and its frequent misdiagnosis as major depressive disorder (MDD) appear to be major problems in patients with BD. Few studies focus on the prevalence of BD and MDD among primary care and psychiatric service patients. In Finland, more than 66% of the population visit a community health care centre during a year; 5% of the population are treated in primary care for a mental disorder, and 3% receive psychiatric treatment (1).

The Finnish Tampere Depression Project (TADEP) was a study that used the Present State Examination (9th version) to assess the prevalence of BD and MDD in primary and secondary care. The Index of Definition cut-off point of > 4 was used to identify cases of BD (ICD-8 diagnosis 296.1). A DSM-III-R assessment was also carried out. The study setting, patients, and data collection methods are reported in detail elsewhere (2,3).

Results

A total of 437 patients in primary care and 435 patients in secondary care were interviewed. In community health centres, the 1-month and 12-month prevalences of BD were 0.9% and 2.1%, respectively. In community mental health centres, the corresponding figures were 4.4% and 7.6%. In

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Medical causes were ruled out, and there were no other implicated medications.

For optimum outcomes, high vigilance is needed to promptly identify the cause of seizures in patients taking psychotropic medications. The reliance of seizure secondary to aripiprazole needs further elucidation.

References


Sandee Grover, MD
Chandigarh, India
Nitin Gupta, MD,
Burton upon Trent, UK
comparison, the 1-month and 12-month prevalence rates of depression were 10.7% and 20.0%, respectively, in primary care, and 49.3% and 56.5%, respectively, in secondary care (3).

Thus, the 1-month and 12-month prevalence rates for depression were 4.8-fold and 3.6-fold, respectively, in primary care and 11.2-fold and 7.4-fold, respectively, in secondary care, compared with the prevalence rates for BD.

Discussion

These results may help in detecting and estimating the proportions of patients with BD in actual clinical practice. However, the possibilities of generalizing from the results are limited, owing to the country-specific health care system. The prevalence and enrichment of BD and unipolar MDD accords with other studies in the sense that BDs represent 10% to 20% of all mood disorders.

References


Marko P Sorvaniemi, MD, PhD
Raimo KR Salokangas, MD, MSc, PhD
Turku, Finland

The Need for More Community Nursing for Adults With Intellectual Disabilities and Mental Health Problems

Dear Editor: We are concerned about the lack of community nursing in our geographical area for adults with intellectual disabilities and mental health problems (that is, a dual diagnosis) and the significant impact this has on our patients and their caregivers. To put this issue into context, individuals with intellectual disabilities are at greater risk than the general population for mental health problems and undiagnosed medical problems.

Psychotropic medications can be highly effective when used to treat specific psychiatric disorders in this population, but they are frequently overused and undermonitored (1). Many individuals are unable to report unpleasant or potentially dangerous medication side effects and depend on caregivers to recognize problems. Caregivers in turn may lack training and skills in the area of medication administration and monitoring for side effects. Community nursing support has been identified as an appropriate and cost effective way to follow these individuals in the community and work with their caregivers, families, and family physicians (2).

Our specialized, interdisciplinary mental health team serves a region with a population of approximately 900 000 adults (3) of whom an estimated 7500 have a dual diagnosis (assuming a 2.25% prevalence rate of intellectual disabilities in the general population and a 38% prevalence rate of psychiatric problems in individuals with intellectual disabilities, 4). We know of 4 full-time nurses who work with this patient population. By comparison, a study in the UK reported a mean of 2.4 community nurses per 100 000 population who were specifically trained to work with adults with intellectual disabilities (5). If we use data from the UK as a reference point, an area our size would support 21.6 such nurses, rather than the present 4.

We contend that enhanced community nursing would ensure better continuity of care for our dual-diagnosis patients and allow increased on-site monitoring and opportunities to educate caregivers about psychiatric disorders and medication effects and side effects. Moreover, it would enable psychiatrists who specialize in dual diagnosis to consult more efficiently with family physicians.

We provide actual case examples to illustrate some of our points.

Case 1

After a patient with challenging behaviour was again referred, the team discovered that the consulting psychiatrist’s recommendation to decrease the patient’s neuroleptic medication, made 2 years earlier to the family physician and shared with the group home staff, had not been carried out. This medication’s side effects contributed to the behaviour that precipitated the second referral. Moreover, the patient’s current staff did not seem to be aware that these recommendations had ever been made.

Case 2

Over a period of several weeks, caregivers had been giving a patient twice the prescribed dosage of neuroleptic medication. The patient experienced severe facial tics and contortions that developed into a serious dystonic reaction. The team was called in because the patient’s behaviour was deemed to be out of control. The facial tics and contortions were not mentioned at the time of the call.

Case 3

Staff called the team because a patient was confused and drowsy, had slurred speech, and was unsteady on his feet. Upon visiting the group home, the team nurse learned that the patient, who was taking lithium, was recovering from a flu-like illness but that his vomiting continued. The nurse found him to be severely dehydrated; she advised staff to discontinue the lithium until the patient’s blood level had been checked and to take him to emergency immediately. Blood work revealed that the patient had lithium toxicity.

We would be interested to hear of the experience of others in regard to these issues.

References


Jane Summers, PhD, CPsych; Judith Adamson, RN; Elspeth Bradley, MB, BS, PhD, FRCPsych, FRCP; Kerry Boyd, MD, FRCP; Stephen Collins, MB, ChB, FRCP; Anthony Levinson, MD, FRCP; Jane Morgan, MD, MHSc, FRCP; Hamilton, Ontario
Improvement in Tardive Dyskinesia With Aripiprazole Use

Dear Editor: We wish to report the case of a patient with tardive dyskinesia (TD) whose improvement with the introduction of aripiprazole is quite similar to a case recently reported in the Journal by Duggal (1).

Case Report
Mrs SR, aged 45 years, was initially diagnosed with bipolar disorder 16 years prior to this report and, more recently, with schizoaffective disorder, bipolar type. She took oral and then depot haloperidol for many years, along with lithium and then divalproex. For 6 years, she was consistently treated in our clinic with risperidone 4 mg and divalproex 2000 mg daily. On 3 occasions, she discontinued all medications, was admitted to the state hospital, and returned to our clinic taking haloperidol decanoate 100 mg intramuscularly every 3 weeks. Each time, we gradually returned her to the risperidone and divalproex combination. On the last occasion, when most recently changed from haloperidol to risperidone, she was noted to have mild TD and an Abnormal Involuntary Movement Scale (AIMS) score of 8. Clonazepam 1 mg daily was added with little improvement. For the next year and a half, her AIMS score varied between 7 and 9, with no trend toward improvement.

In December 2003, her family took her to see a physician in Mexico, who recommended that she stop all psychiatric medications and who gave her an unknown drug or drugs to take in their place. She was apparently without her usual medications for no more than 10 days. Upon her return to the US, her TD had worsened dramatically, and her AIMS score was 26. Risperidone and divalproex were immediately restarted, but no improvement in TD occurred over the next 4 weeks. Finally, aripiprazole 15 mg daily was added to her other medications. Within 3 days, choreoathetosis was dramatically reduced, and 1 week after starting aripiprazole, her AIMS score was 7.

Like Duggal, we speculate that the partial agonist status of aripiprazole may offer a unique remedy for some patients who develop TD after prolonged use of first-generation antipsychotics, particularly when substitution of a second-generation antipsychotic does not reduce TD severity (2). We are somewhat reassured that the preclinical data available for aripiprazole seem to argue against progressive hypersensitization of D2 receptors with prolonged exposure (3,4).

Finally, we note the ratchet-like impact on the severity of our patient’s TD of briefly discontinuing risperidone and divalproex. We initially anticipated that resuming her usual medications would at least substantially undo the abrupt increase in TD. No such improvement was seen over a period of 4 weeks, prior to the addition of aripiprazole. We have found no reference in the literature either to such an abrupt and dramatic worsening of TD after brief discontinuation of a second-generation antipsychotic or to its failure to improve following reinstitution of the same drug.

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References

James K Witschy, MD
A Scott Winter, MD
Fort Worth, Texas

Books Received

The following books have been received; the courtesy of the sender is acknowledged by this listing. Books of particular interest to readers of the Journal will be reviewed by selected individuals. Not all books are available for review.


