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Antidepressants and upper gastrointestinal bleeding

New results suggest a link

General practice
p 1106

Is there an increased risk of upper gastrointestinal bleeding associated with antidepressant therapy? Most clinicians probably think this unlikely. Indeed, despite spontaneous case reports,[1–3] most drug reference sources, including the *British National Formulary* and the *Data Sheet Compendium*, do not mention any such association. In this issue, however, de Abajo et al report that there is indeed an increased risk with selective serotonin reuptake inhibitors (p 1106).[4] Moreover, they suggest a possible interaction with non-steroidal anti-inflammatory agents, leading to an increased risk far beyond a simple additive effect. How robust are these results and what are the implications for clinical practice?

Retrospective observational studies are always subject to confounding, and the present case-control study is no exception. However, this study seems to be less prone to it. Upper gastrointestinal bleeding is not generally known to be associated with serotonin reuptake inhibitors, so channelling bias[5] is less likely. The more obvious possible confounders were carefully adjusted for and the database used is respected for the quality of its data. Therefore, despite the possibility of confounding, the weight of evidence suggests that there is an increased risk of upper gastointestinal bleeding with some antidepressant compounds and that this risk is increased if the patient is also taking non-steroidal anti-inflammatory drugs.

More detailed implications for practice are harder to tease out. The authors started off with a seemingly plausible biochemical hypothesis that, since serotonin is important in the haemostatic response to vascular injury, its depletion from platelets by the serotonin reuptake inhibitors may increase the risk of bleeding.[4 6] The data they obtained are broadly consistent with this hypothesis. However, uncomfortable inconsistencies remain. The authors' classification of clomipramine as a serotonin reuptake inhibitor may cause some surprise but has a sound biochemical basis. Clomipramine's serotonin selectivity of about 130, relative to norepinephrine, is close to those of fluoxetine and paroxetine but higher than that of trazodone (see table on www.bmj.com).[7] Even imipramine's selectivity is not far off that of trazodone (27 versus 53). Indeed, except for nortriptyline and lofepramine, the tricyclic antidepressants shown in the table are serotonin reuptake inhibitors, based on the more recent radioligand binding assays using cloned human transporters.

Therefore, it would be inappropriate to infer that serotonin reuptake inhibitors may increase the risk of upper gastrointestinal bleeding without first defining what we mean by a serotonin reuptake inhibitor. Structural classification (tricyclics) and biochemical classification (serotonin reuptake inhibitors) clearly clash. If a serotonin effect on haemostatic response is the proposed mechanism for the adverse effect, should we not focus on the size of the dissociation constants for the serotonin transporter rather than, or at least as well as, the selectivity? Doing so reveals other inconsistencies. For example, trazodone is associated with the highest risk of upper gastrointestinal bleeding. Yet it appears to be an outlier among the serotonin reuptake inhibitors with respect to the serotonin equilibrium constants, although the 95% confidence interval for the adjusted relative risk was wide. The authors obtained a pooled relative risk, associated with current use of a serotonin reuptake inhibitor only (fluoxetine, fluvoxamine, paroxetine, sertraline, and clomipramine), of 2.6 (95% confidence interval 1.7 to 3.8) with a corresponding figure of 3.7 (3.2 to 4.4) for those currently using non-steroidal agents only. Concurrent use of both types of drugs yielded a relative risk of 15.6 (6.6 to 36.6).

Should prescribing practice be changed on the basis of these new data? Greater caution is probably warranted in co-administering non-steroidal anti-inflammatory drugs and serotonin reuptake inhibitors, including clomipramine, particularly for patients with risk factors for upper gastrointestinal bleeding. When both classes of drugs are judged necessary, there is better evidence on the choice of a non-steroidal agent[8] than on the choice of a serotonin reuptake inhibitor, or indeed any antidepressant, for reducing the risk of bleeding. For example, changing from indomethacin to low dose ibuprofen is likely to reduce the risk more than changing from paroxetine to imipramine. Whether paroxetine was preferable to imipramine and indomethacin to ibuprofen in the first place is another debate. With greater clinical experience and validation, the newer COX-2 selective non-steroidal anti-inflammatory agents may make a contribution.

There is an increasing tendency in drug evaluations to lump drugs together, often as part of meta-analyses, to come up with a prized "class effect." Tatsumi et al[7] and de Abajo et al[4] remind us indirectly that great care is necessary when doing so. An antihistamine or a tricyclic drug may be a serotonin uptake inhibitor and vice versa. Just like patients, drugs act as individual agents, each with its own three dimensional and electronic structure to exert unique effects on three dimensional receptors.[9 10]

website *e*xtra

The table appears on the BMJ's website

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Though the general practice database used by de Abajo et al is useful, it may fail to capture all events[11] and is not fully representative of prescribing practice. It certainly does not capture self medication adequately. Over the counter antihistamines such as chlorpheniramine and diphenhydramine, which bind to the serotonin transporter and show selectivity towards it, and COX inhibitors, such as aspirin and ibuprofen, are widely used. Such use may confound estimates of risk. Therefore, further studies using alternative methods are necessary to confirm these results.

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1 Yaryura-Tobias JA, Kirschen H, Ninan P, Mosberg HJ. Fluoxetine and bleeding in obsessive-compulsive disorder. *Am J Psychiatry* 1991;148:949.
2 Bruising and bleeding with SSRIs. *WHO Adverse Drug Reaction Newsletter* 1998:3.
3 Yue Q-Y, Abdi YA. SSRI och blödningsrisk. *Info från Läkemedelsverket* 1998;8:5-7.
4 De Abajo FJ, García Rodríguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control stury. *BMJ* 1999;319:1106-9.
5 Petri H, Urquhart J. Channelling bias in the interpretation of drug effects. *Stat Med* 1991;10:577-81.
6 Li N, Wallén NH, Ladjevardi M, Hjemdahl P. Effects of serotonin on platelet activation in whole blood. *Blood Coag Fibrinolysis* 1997;8:517-23.
7 Tatsumi M, Grosham K, Blakely RD, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur J Pharmacol* 1997;340:249-58.
8 Henry DA, Lim LL-Y, Garcia Rodriguez LA, Guttman PS, CarsonJL, Griffin M, et al., Variability in risk of gastrointestinal complication with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996;312:1563-6.
9 Li Wan Po A. Designing safe drugs with safety in mind. *Adverse React Toxicol Rev* 1998;17:60-2.
10 Shah RR, Midgley JM, Branch SK. Stereochemical origin of some clinically significant drug concerns: lessons for future drug development. *Adverse React Toxicol Rev* 1999;17:145-90.
11 Hawkey CJ. Omeprazole and bleeding peptic ulcer, or "How case-control studies can tell you what you suspected all along." *Epidemiology* 1999;10:211-3.

Carbon monoxide poisoning

Is still an underrecognised problem

The onset of autumn and cooler weather traditionally heralds the start of another season in the northern hemisphere—the peak incidence of unintentional deaths from carbon monoxide. Each year around 50 people in the United Kingdom die from carbon monoxide poisoning, and a year ago the chief medical officer warned again of the dangers.[1] As yet there is no evidence that the population is at any lesser risk.

Humans have been poisoned by carbon monoxide since they first discovered hydrocarbon fuels, incomplete combustion of which is the usual cause of poisoning. Napoleon's surgeon, Larrey, saw soldiers with carbon monoxide induced myonecrosis when billeted in huts heated by woodburning stoves. And over 60 years ago American physicians were warned that chronic carbon monoxide exposure could mimic many neurological conditions, such as "cerebral haemorrhage, encephalitis, multiple sclerosis, spastic paraplegia, chorea and tetany."[2] Throughout the world people continue to die unnecessarily from carbon monoxide exposure or to survive their encounter with disabling symptoms whose cause is misdiagnosed.

Carbon monoxide famously binds to haemoglobin over 200 times more strongly than oxygen, a strange evolutionary quirk explained by the tiny amounts of carbon monoxide produced naturally in the body by haem oxygenase and the need to have an efficient scavenging system for such a toxic substance.[3] Although the carboxyhaemoglobin which results from inhaling the gas is an indicator of exposure, clinical features may persist or begin long after the disappearance of measurable carboxyhaemoglobin, which has a half life of only four to five hours when clean air is breathed. Displacement of oxygen from haemoglobin is merely the best known property of carbon monoxide, which poisons the body in many more subtle and complex ways.

Carbon monoxide interferes with other ferroproteins such as myoglobin and various enzymes including members of the cytochrome family.[4] Studies suggest that endogenous carbon monoxide may share properties with nitric oxide, such as smooth muscle relaxation and altered platelet aggregation, and be intimately linked with nitric oxide dependent reactions, which if unregulated can lead to cellular death. Oxidative damage to neurovascular epithelium produced by carbon monoxide causes increased leucocyte adherence and subsequent peroxidation of brain lipid.[5 6]

The central nervous system is thus especially vulnerable, with areas at arterial "watersheds"—such as the medulla and basal ganglia—at particular risk.[1] The damage can be shown radiologically.[7] Isolated neurological symptoms such as gesture apraxia and single seizures have been ascribed to carbon monoxide poisoning, as has "winter headache." A delayed neurological syndrome,[8] which may mimic almost any neuropsychiatric complaint, though impaired motor control is usually a prominent feature, has been reported up to 80 days after carbon monoxide exposure. Yet this syndrome is both preventable and treatable if the true cause is recognised.[9]

Economics and geography, as much as pathology and biochemistry, determine someone's susceptibility to carbon monoxide poisoning. Korea's population is slightly smaller the United Kingdom's, yet 20 years ago there were around 3000 deaths and a million admissions a year,[10] and by 1982, 300 hospitals were equipped with hyperbaric oxygen facilities. Korean houses are still commonly heated by a large coal brick dropped into a space beneath the living area. Horizontal "chimneys" pass under other rooms in the house to provide heat, and several dwellings often share a final common flue.

In Chesterfield recently a family of four and their elderly neighbour died because the common chimney

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