The findings of this study suggest that even if a new drug is associated with lower side effects than previous drugs in its class at the patient level, a marked increase in its use can be associated with an apparently paradoxical adverse impact on the population.

Contributors: MM, DNJ, GN, PCA, and AL designed the study; MM, DNJ, PCA, and AK did the study. GN, PCA, and AL advised and supervised. PCA gave statistical advice. MM is guarantor.

Funding: MM is supported by a New Investigator award from the New Emerging Teams of the Canadian Institutes of Health Research (CIHR). DNJ is supported by a New Investigator award from the CIHR and by the University of Toronto Drug Safety Research Group. GN is supported by the Mary Trimmer Chair in Geriatric Medicine Research at the University of Toronto. AL is a senior scientist of the CIHR. This study was supported by a CIHR operating grant (MOP-49527) and a CIHR Chronic Disease New Emerging Team programme grant (NET-54010). The NET programme receives joint sponsorship from the Canadian Diabetes Association, the Kidney Foundation of Canada, the Heart and Stroke Foundation of Canada, and the CIHR Institutes of Nutrition, Metabolism and Diabetes and Circulatory and Respiratory Health.

Competing interests: MM has done research in an unrelated content area upon the request of an academic institution whose funding was supported by Pharmacia in the past three years, but none of the funding for this study was provided by any pharmaceutical company.

Ethical approval: Sunnybrook and Women's College Health Sciences Centre Ethics Review Board.

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(Accepted 22 January 2004)

doi 10.1136/bmj.38068.716262.F7

DRUG POINTS

Nose bleeds associated with use of risperidone

Mira Harrison-Woolrych, David W J Clark

Intensive Medicines Monitoring Programme, New Zealand Pharmacovigilance Centre, Department of Preventive and Social Medicine, University of Otago, New Zealand

Mira Harrison-Woolrych *director*

David W J Clark *senior research fellow*

Correspondence to: M Harrison-Woolrych, PO Box 913, Dunedin, New Zealand
Mira.harrison-woolrych@stonebow.otago.ac.nz

BMJ 2004;328:1416

The New Zealand Intensive Medicines Monitoring Programme has received two reports of nose bleeds associated with risperidone. A 57 year old woman began having profuse nose bleeds associated with headaches immediately after starting to take risperidone 1 mg daily. She had no history of hypertension and was taking no other medicines. Risperidone was discontinued four days later and the nose bleeds stopped. A 42 year old man with no history of nose bleeds began having spontaneous nose bleeds while taking risperidone; coagulation tests were reported as normal.

The World Health Organization's international drug monitoring database contained an additional 54 reports of nose bleeds associated with risperidone, of which 37 had sufficient information for causality assessment. In 22 cases, nose bleeds began within three weeks of starting risperidone. In 10 of 12 patients for whom dechallenge data were available the reaction abated on stopping risperidone. Three of the 10 patients underwent rechallenge: two did not have nose bleeds again, but the third, a 15 year old boy, had a recurrence after the rechallenge.

Several pharmacological mechanisms might explain this adverse reaction. Thrombocytopenia is a recognised adverse effect of atypical antipsychotic medicines and has been reported with risperidone.[1] Although one of the New Zealand patients was reported to have a normal blood count, in nine of the 37 WHO cases thrombocytopenia was reported.

Risperidone is also a potent 5-HT_2A receptor antagonist. Sarpogrelate, another 5-HT_2A antagonist, increases blood flow in the coronary microcirculation by reducing platelet aggregation and vasoconstictor release from platelets.[2] Risperidone could plausibly have a similar effect in other parts of the microcirculation.

The New Zealand and UK product information for risperidone does not mention nose bleeds. The US *Physicians Desk Reference* states that in premarketing studies nose bleeds occurred in 1 in 100 to 1 in 1000 patients.[3] Literature searches did not identify any reports of nose bleeds associated with risperidone, and so we believe these are the first published cases of this adverse drug reaction.

Contributors: MH-W assessed the original New Zealand case reports, performed the literature searches, identified the signal, and wrote the manuscript. DWJC accessed and evaluated the cases from the World Health Organization's database, proposed a possible mechanism, and reviewed the manuscript.

Funding: The Intensive Medicines Monitoring Programme receives most of its funding from New Zealand's Ministry of Health.

Competing interests: None declared.

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Endpiece

The end of the party

The closing years of life are like the end of a masquerade party, when the masks are dropped.

Arthur Schopenhauer (1788-1860), German philosopher

Fred Charatan, retired geriatric physician, Florida