Comment on: Serotonin syndrome due to co-administration of linezolid and venlafaxine

P. Ken Gillman*

Department of Clinical Neuropharmacology (DCNP), Pioneer Valley Private Hospital, PO Box 8183, Mount Pleasant, Queensland 4740, Australia

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*Tel: +61-7-4942-1883; Fax: +61-7-4942-8283;
E-mail: kg@matilda.net.au

Sir,
The report of Jones et al.1 concerning serotonin syndrome (SS) with linezolid follows several other reports (referenced by the authors), one of which I have already commented on.2 Recent advances have improved our understanding of SS [better called serotonin toxicity (ST)3]. Professor Whyte’s group at the Hunter Area Toxicology Service (HATS) have published their seminal studies of a large number of overdoses, many (>500 cases) involving serotonergic drugs. Their papers on ST4–6 define the features and reinforce the value and importance of the spectrum concept.7,8 It is a complex subject: up-to-date and comprehensive information can be accessed in my web update9 [particularly, a list of drugs that are significant serotonin reuptake inhibitors (SRIs)].

The important conclusion from Whyte’s work is that ST is a spectrum and potentially fatal ST only occurs when monoamine oxidase inhibitors (MAOIs) are mixed with SRIs. If general physicians understand which drugs are SRIs and exercise caution if they have to be combined with linezolid (which may possibly be an MAOI of significant clinical potency) then they are unlikely to encounter serious clinical problems. SRIs that may not be readily identified as such include some of the narcotic analgesics (tramadol, pethidine), ‘dual action’ antidepressants like duloxetine, venlafaxine and milnacipran (and the similar drug venlafaxine), as well as the anti-histamines chlorpheniramine and brompheniramine.

The usual features of ST6,8 are:

(i) neuromuscular hyperactivity: tremor, clonus, myoclonus, hyperreflexia and (in the advanced stage) hyperton/ pyramidal rigidity;
(ii) altered mental status: agitation, excitement (with confusion only in the advanced stage);
(iii) autonomic hyperactivity: diaphoresis, fever, mydriasis, tachycardia and tachypnoea.

It may be noted that the reported case is atypical and exhibits mild ST signs; this may be attributed to increased susceptibility due to old age and organic brain disease. Venlafaxine produces greater ST than the selective SRIs (SSRIs)5 and can give rise to severe serotonergic side effects by itself in therapeutic doses, and ST in overdose. This is where the spectrum concept is useful. All the SSRIs can produce ST; HATS data show that it occurs in ~15% of cases where an overdose has been taken.4 Case reports of exaggerated serotonergic side effects and ST from monotherapy with serotonergic antidepressants (in therapeutic dose) are well documented and have been reviewed.10

Case reports like this cannot therefore be taken as evidence that linezolid is involved in ST of only mild to moderate severity. If it is able to produce clinically significant monoamine oxidase inhibition then there will be a risk of severe and life-threatening ST if it is co-administered with any SRI. The pressor response of linezolid to oral tyramine is similar to that of moclobemide.11 Moclobemide frequently causes serious ST, and sometimes deaths, but only when combined with SRIs. The MAOI activity of linezolid may possibly reach levels sufficient to precipitate serious ST, so continued vigilance is advisable despite the absence of ST with SRIs in the small Phase 3 study.12

Ceasing only the venlafaxine may have been an option in this case because, like moclobemide, linezolid alone will not cause ST, but venlafaxine alone does. Dissemination of accurate information about ST will assist treatment decisions about linezolid, and improve understanding and risk estimation of ST.

References

Sir,

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a worldwide, firmly established healthcare-associated pathogen. Risk factors for MRSA include recent hospitalization or surgery, nursing home residence, renal dialysis and exposure to invasive medical devices. Recently, cases of MRSA have been identified in healthy community-dwelling persons without risk factors for MRSA acquisition. Such community-acquired (CA) MRSA infections have been reported in Australia, New Zealand, Canada, the USA and Europe. Here, we report the first case of CA-MRSA in Hong Kong.

In May 2004, a 50-year-old man presented to the Accident and Emergency department of a regional hospital with a 1 week history of a carbuncle at the back of his neck. It measured 4 cm in diameter and there was purulent discharge from the lesion. At presentation, he had a tympanic temperature of 38°C. The attending doctor performed an incision and drainage. A deep wound swab of the pus was sent for bacterial culture. The patient was discharged with a 7 day course of oral ampicillin and clocloxacillin. Aerobic and anaerobic culture of the pus yielded acid, ciprofloxacin, co-trimoxazole, tetracycline, chloramphenicol, rifampicin and vancomycin. Following identification of the non-multiresistant MRSA, the patient was contacted by phone for further information. Direct questioning confirmed that risk factors for healthcare-associated MRSA were absent. The patient enjoyed good past health. There was no history of hospitalization, surgery, dialysis or residence in a nursing home in the previous 18 months. He had no history of exposure to persons at risk for MRSA. None of his family members were healthcare workers. Following discharge, the neck wound gradually healed without the use of other antibiotics.

The presence of the *mecA* gene in the isolate was investigated by PCR. The staphylococcal chromosomal cassette type (SCCmec) including *mecR1, mecI* and the chromosomal cassette recombinase *ccr* genes were evaluated using specific primers described by Lim *et al.*

PCR for *mecA* was positive. With primers specific for the membrane-spanning domain of *mecR1* was positive, whereas those for the penicillin-binding domain of *mecR1* and *mecI* were negative. The isolate amplified with type 2 *ccr* gene complex primers but not with primers for type 1, 3 and 4 *ccr* genes. The result indicates the presence of SCCmec-type IV in this CA-MRSA strain. In order to identify the genetic background of this strain, the organism was characterized by multilocus sequence typing (MLST). Specific primers described for *arc, aro, glp, gmk, pta, tpi* and *yqi* were used to amplify internal fragments (size 402–516 bp) of seven housekeeping genes. The amplified products were purified and sequenced in both directions. Conditions for amplification of the seven loci and sequence interpretation were those described on the MLST website. This strain has an allelic profile 2-2-2-2-6-3-2, corresponding to ST30. According to Vandenesch *et al.*, ST30 represents the most frequent ST of CA-MRSA in the Southwest Pacific. In Hong Kong, typing studies have not been performed on healthcare-associated MRSA isolates from the whole territory. In an analysis of strains from one hospital, it was reported that the predominant PFGE types belong to one group and fall in the same cluster as EMRSA-1, -4, -7, -9, and -11 isolates. Preliminary MLST and SCCmec analysis by the same group suggest that representative isolates are related to ST239-MRSA-III (allelic profile for ST239 is 2-3-1-1-4-4-3).

The present case has several features common to CA-MRSA reported elsewhere. First, established risk factors for healthcare-associated infections are absent. Second, the strain is not multiresistant. Third, this strain carries SCCmec type IV, which is the smallest methicillin-resistance locus among the four known types. Unlike other SCCmec elements, SCCmec IV does not encode additional resistance determinants other than the *mecA* gene, which may explain the non-multiresistance characteristic of CA-MRSA. Fourth, the MLST analysis showed that the genetic background of our strain did not correspond to that of the major pandemic healthcare-associated MRSA clones.

In conclusion, this report adds to the expanding distribution of CA-MRSA infections. As yet, the origin and the factors that contribute to their emergence are poorly understood. If community strains continue to spread, this will add to the pressing public health threat from this pathogen.

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