Tramadol revisited

‘To be great is to be misunderstood’
  Ralph Waldo Emerson, 1803–1882
‘Tis hard to say, if greater want of skill appear in writing
or in judging ill’
  Alexander Pope, 1688–1744

Since its launch in the UK in 1994, tramadol hydrochloride
(Zydol-Searle, Zamadol-Asta, Tramake-Galen) has received
a mixed reception in the medical press.1-3 However, more
evidence has now accumulated which clarifies both the way
in which this interesting compound produces analgesia and
its clinical applications.

While initially considered to be a weak opioid, the adverse
effect profile of tramadol appeared to be atypical
of a pure opioid agonist and this led to the discovery of its
multimodal mechanisms of action. More complete data
have been produced, in both animals and humans, of the
effect of tramadol on the release of monoaminergic
neurotransmitters in the central nervous system and its
agonist action at peripheral and central opioid receptors. It
is now accepted that in addition to a mu-opioid agonist
effect, tramadol enhances the function of the spinal des-
cending inhibitory pathway by inhibition of reuptake of both
5-hydroxytryptamine (5-HT) and norepinephrine, together
with presynaptic stimulation of 5-HT release.4,5 Desmoules
and co-workers have confirmed in humans that the analgesic
effect of tramadol is apportioned between the opioid and
monoaminergic components.6 The analgesic effect produced
by the racemic mixture that is commercial tramadol is a
synergistic interaction of the two enantiomers and their
differing modes of action.5

Tramadol is metabolized by the cytochrome P450 enzyme
system in the liver to form 11 metabolites, of which M1
(O-desmethyltramadol) predominates and possesses anal-
gesic properties. The O-demethylation to M1 depends on
the enzyme sparteine oxygenase, CYP2D6 (P4502D6). The
role of M1 in producing analgesia has been evaluated by
comparing analgesic efficacy in human volunteers known
to be CYP2D6 deficient (as are 8% of Caucasians) with
normal subjects who are extensive metabolizers. Tramadol
showed measurable but reduced analgesia in the poor
metabolizers, suggesting that the M1 metabolite may con-
tribute to analgesic efficacy. This contrasts with complete
absence of analgesia in the same group of poor metabolizers
after codeine administration.7

The published intraoperative experience with tramadol
has been very limited, no doubt because of concerns after
the report in 1986 of increased recall of intraoperative events
with the use of tramadol administered in the peroperative
period.5 However, this study was based on the now out-
moded oxygen–nitrous oxide–opioid anaesthetic technique
and more recent studies using sophisticated awareness/
recall and electroencephalographic depth of anaesthesia
techniques have shown that tramadol has no clinically
significant effect on contemporary, volatile, isoflurane-based
anaesthesia.9 10 It would appear, therefore, that in the
presence of adequate depth of anaesthesia, as practised
currently, intraoperative administration of tramadol does
not result in accidental awareness and this is reflected in
changes to the UK tramadol data sheet.

The role of tramadol as an intraoperative analgesic has
been evaluated in both in-patient and day-case studies,
showing no instances of intraoperative cardiorespiratory
adverse sequelae or accidental awareness. More rapid and
complete recovery from general anaesthesia with improved
postoperative adverse effect profiles have been reported
compared with those studies where tramadol was admin-
istered as a loading dose when the patient had regained
consciousness. For acute pain of moderate to severe inten-
sity, increasing numbers of studies are showing that tramadol
3 mg kg–1 would appear to be the most suitable initial
dose.11-16 A marked reduction in postoperative shivering
has also been noted in patients receiving tramadol.14 16 In
addition, the significant value of its minimal respiratory
depressant effect continues to be emphasized.17 18

The benefit of tramadol in day-case surgery was exempli-
fied in a study of 228 patients undergoing surgery through
a groin incision. Tramadol administered during and after
operation was compared with the combination of intraoper-
ative fentanyl and postoperative co-codamol.12 In these
relatively painful procedures, tramadol provided superior
analgesia on the day of discharge when pain would likely
be maximal. The adverse effect profile in each group was
similar but tramadol was responsible for fewer unplanned
in-patient admissions than the fentanyl–co-codamol mixture,
although this finding was not statistically significant.

In moderately painful surgery, tramadol has been shown
to be ‘an effective analgesic in postoperative pain’.3 The
18 studies quoted by McQuay and Moore showed that all
doses of tramadol were satisfactorily superior to placebo in
both post-surgical and dental pain, and there was a signifi-
cant dose–response effect. Headache, nausea, vomiting, dizzy-
ness and somnolence were the most commonly reported
adverse events, although they were predominantly of mild
intensity. Their occurrence after the treatment of dental
surgery pain was significantly higher than that after other
types of surgery, possibly related to the ‘acute’ dosing in
awake patients and rapid mobilization.3
Paediatric analgesia is seen frequently as a challenge and the use of tramadol has been shown to be beneficial when administered by standard or by less well used routes.\textsuperscript{19–21} The use of tramadol in children, which is not yet licensed in the UK for those less than 12 yr of age, shows great promise and its potential may be at present underestimated. There is considerable experience with the agent internationally in children greater than 1 yr, and further work is needed to evaluate its true potential.

In the treatment of chronic pain, contemporary studies have shown that effective analgesia can be achieved with tramadol in a wide spectrum of painful pathologies, particularly in osteoarthritis, fibromyalgia and diabetic neuropathy, used orally and intra-articularly.\textsuperscript{22–25} Further benefit has been gained by the introduction of an oral, sustained release formulation of tramadol. Not only is patient compliance improved but the incidence of adverse effects compared with instant release preparations is reduced significantly.\textsuperscript{26} There would also appear to be a place for tramadol in the field of palliative medicine to the extent that it has been included in the second edition of the WHO recommendations for cancer pain treatment.\textsuperscript{26–28} The reduced constipating effect of tramadol compared with other opioids is a useful asset in this area of practice.\textsuperscript{29}

While variation in the occurrence of adverse effects from tramadol is wide, patterns of causation, prevention and treatment are emerging. Very early ambulation after i.v., post-surgical tramadol is likely to produce nausea and dizziness while administration of the same dose, well before emergence from anaesthesia, allows the patient to awaken pain free and with a low occurrence of adverse effects.\textsuperscript{30} As a standard dose, tramadol 3.0 mg kg\textsuperscript{–1}, given at induction of anaesthesia, does not obtund the pressor response\textsuperscript{31} and onset time is relatively slow.\textsuperscript{32,30} The optimum time for the initial tramadol loading dose may be immediately after commencement of surgery following the use of a short-acting opioid to cover induction of anaesthesia and surgical incision.

To achieve a minimal incidence of adverse effects with chronic oral administration, therapy should be commenced at the lowest dose and increased gradually, titrating patient response against dose.\textsuperscript{32,33} Commencing treatment with tramadol in this manner appears to result in a low incidence of adverse effects and, should they occur, generate the onset of tolerance to them in the shortest time. It is suggested that the prevention or treatment of the common, opioid-like adverse events can be with phenothiazine derivatives (dopamine antagonists) or 5-HT\textsubscript{3} receptor block.\textsuperscript{34}

However, there remain at least three contentious areas: interaction of tramadol with coumarin anticoagulants, occurrence of drug-induced seizures and abuse liability. The interaction of tramadol with oral anticoagulants of the coumarin variety with the end result of prolongation of the International Normalized Ratio (INR) has been reported.\textsuperscript{35,36} However, more recent work has failed to confirm these findings.\textsuperscript{37,38}

After 2 yr availability of tramadol in the UK, 27 reports of convulsions, possibly caused by tramadol, had been reported to the Committee on Safety of Medicines (CSM), a reporting rate of 1 in 7000. The majority of these patients were receiving epileptogenic agents in addition to tramadol and several of the others had received large i.v. doses of tramadol.\textsuperscript{39} Data from the UK-based General Practice Research Database identified 10 916 patients who had received more than 30 000 prescriptions for tramadol over a 22-month period, the most frequent dose being 50 mg 3–4 times daily. The study identified 17 patients who experienced idiopathic incident seizures (11 had definite seizures and six were possible cases). All (17) had received other drugs in addition to tramadol in the previous 90 days: opioids (eight patients), tramadol and opioids (five), other analgesics (three) or no analgesic (one). The conclusion was that there was no risk of idiopathic seizures associated with tramadol therapy alone.\textsuperscript{40} However, tramadol should not be used in epileptics and should be used with caution in patients on concomitant medication which lowers seizure threshold.

The abuse potential of tramadol requires more data for an accurate picture to emerge. In the USA, 247 instances of abuse were described out of an estimated 16.5 million patient exposures to tramadol in 2.5 yr (1995–1997), equivalent to 1.5 per 100 000. By late 1997, the rate had declined to less than 1:100 000.\textsuperscript{41} However, Federal Drug Administration (FDA) values were somewhat higher; in 1996, there were 1203 reports of abuse but a proportion of these may have included cases of opioid withdrawal. UK figures for 1994–5 detailed five reports of drug dependence and 28 of withdrawal.\textsuperscript{39}

Tramadol is now established in several clinical roles, usefully blending a reasonable, dose-related efficacy with a relative lack of respiratory depression, major organ toxicity or abuse potential. It is of particular value in NSAID-intolerant patients, the elderly and for those undergoing day-case surgery. Although the literature concerning tramadol continues to grow apace, not all questions have been answered. Further evaluation, especially in contentious areas, needs to be forthcoming. Its role in the long-term management of persistent pain also remains to be demarcated accurately.

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