

## Dextropropoxyphene is dead? Long live....

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On 20 April 2011, the Medicines Control Council (MCC) announced its decision to withdraw all dextropropoxyphene (DPP-) containing products from the South African market within three months, because of stated safety risks and an insufficiently weighted risk-benefit profile. These risks refer to dose-related cardiac conduction abnormalities associated with QT prolongation, provoked by the main metabolite of DPP, norpropoxyphene. Cases of fatal arrhythmias have been described. Drugs affected include:

- Distalgesic®;
- Doloxene® and Doloxene® Co-65;
- Lentogesic®;
- Synap Forte® (24% of the postoperative oral analgesic market in South Africa); and
- Doxyphene®;

The developments regarding DPP have received considerable media prominence, on a scale approaching that of the Vioxx® drama. There are other similarities between the two situations:

- We may now have been deprived of really useful “first-choice” or “default” oral analgesics.
- Competitor companies and others with vested interests were interested parties.
- The media were used to promote agendas.
- Completely conflicting data were presented by the protagonists in both cases.
- Complications associated with chronic use in susceptible patients were extrapolated to apply to acute use in the otherwise healthy patient. There may, therefore, be an element of “legislating against stupidity”.
- The pharmaceutical industry was forced to revisit the science and evidence underlying the complications. This was a good thing, particularly regarding older drugs that were granted regulatory registration when criteria may not have been as stringent as they are today.
- We were forced to think about the drugs we use, and their constituents, rather than resorting to “knee-jerk” prescribing.

Withdrawal of DPP, another major frontline analgesic, has dealt a crippling blow to the practice of analgesia, which is already suffering from a diminishing therapeutic

armamentarium. Pain is multifocal in origin and demands a multimodal and multi-targeted response. We need safe and effective analgesia to send home with the patient.

### History of the DPP debacle

Weak opioids (DPP, codeine and, more latterly, tramadol) have been components of acute and chronic pain therapy regimens since the 1950s. DPP has been used in hundreds of millions of patients since it became available, with 23.3 million prescriptions originating in the USA alone in 2007. Whilst abuse has certainly occurred and fatalities have been described, as would be expected with opioids, these phenomena have largely been associated with prolonged use in the chronic pain setting, in alcohol- and drug-dependent patients. It is likely, but remains unproven, that many of the deaths reported do, indeed, relate to malignant cardiac arrhythmias. No deaths have been described with the use of any of the DPP-containing drugs in South Africa, when these were used at standard doses in the acute pain setting. One would expect a strongly discernible safety signal if DPP were a high-risk drug in these patients, given the vast number of patients who have received DPP-containing drugs.

Nonetheless, in 1979, cases of abuse and mortalities associated with DPP provoked a petition presented to the Food and Drug Administration (FDA) for the withdrawal of DPP-containing drugs from the US market. At this time, response to the petition was as follows:

- The FDA was unable to conclude that DPP-associated deaths were related to the “cardiotoxic” effects of the metabolite, because of the absence of evidence.
- The FDA was unable to identify any cases of death or serious cardiac events associated with DPP taken at standard dosages.
- The FDA found that DPP misuse was associated with a risk of death that was mostly related to overdose suicide attempts.
- As for questions regarding the analgesic efficacy of DPP, the FDA noted that:
  - As a single agent, DPP is not superior or inferior to full doses of paracetamol; but

- DPP confers additive analgesic efficacy when combined with aspirin, paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs); and
- Paracetamol, aspirin and NSAIDs are associated with toxicity at high doses at a greater frequency than DPP.

The petition was, therefore, declined, and DPP-containing drugs remained on the market. Indeed, many more formulations were registered.

The issue resurfaced in around 2005 in the UK, where the regulatory authority ordered the phased withdrawal of co-proxamol from the market as it was implicated in 300–400 suicides annually, and this risk outweighed any analgesic benefit. DPP alone was implicated in only 1.2% of these suicides and the majority of these patients used multiple drugs. The drug was withdrawn on 31 December 2007, triggering a surge in unlicensed imports. Three substantial differences exist between DPP abuse in the UK and most of the rest of the world:

- In the UK, the drug was available as a hydrochloride salt, and elsewhere predominantly as a napsylate. This had implications regarding the absorption, peak effect and onset time.
- The UK dose of DPP was 32.5 mg per tablet (about two-thirds of the clinically effective dose), hence there was poor analgesic performance in comparison with other pharmacological options.
- Unlike in the rest of the world, where DPP is a scheduled drug, before 2005, DPP was sold in the UK as an over-the-counter (OTC) medicine and without prescription.

Events in the UK and ongoing reports of intentional and accidental fatal outcomes related to DPP use provoked re-examination of the registration of DPP by the FDA in 2006, the European Medicines Agency in 2009, and the MCC in 2010. Very little new evidence had surfaced since 1979, but the process was gathering momentum. A small, statistically frail study showing evidence of QT prolongation at “standard dosages”, as well as further studies questioning the efficacy of DPP in comparison to other oral analgesics, led to the conclusion that the benefits of DPP do not outweigh its risks. All the regulatory agencies, therefore, recommended a phased withdrawal of DPP-containing drugs. It was concluded that tightening the scheduling, limiting the size of packs and issuing warnings and advisories would still not guarantee adequate protection of public health. Incidentally, it should be noted that none of the weak oral opioids (DPP, codeine or tramadol) was found individually to outperform full doses of paracetamol or ibuprofen.

In South Africa, the decision has been appealed and is, therefore, on hold until a full investigation is completed... which could take a very long time. So, we can continue to prescribe DPP, albeit in a potentially medico-legally hostile environment. It is of interest to note that France and Australia

have declined to follow the European recommendations, as they found no evidence of excess cardiovascular risk or high suicide potential at registered doses and current scheduling restrictions (identical to those in South Africa).

### DPP pharmacology in brief

DPP is a weak oral opioid with moderate analgesic efficacy. It is structurally similar to methadone and has a half-life varying from six to 12 hours, depending on patient age and creatinine clearance. Steady-state concentrations are only achieved by about 48 hours after onset of therapy. Accumulation of DPP is, therefore, possible with six-hourly dosing in frailer patients.

The maximum safe dose of DPP is < 500 mg/day in healthy patients. The lethal dose ( $LD_{50}$ ) is 20mg/kg/day, which is equivalent to 30 Synap Forte® tablets. Interestingly, the lethal dose of Stopayne® or Tramal® is also in the order of 30 tablets/capsules.

DPP is not considered safe in pregnancy, paediatric patients and patients with porphyria. It tends to produce less constipation and nausea than other weak oral opioids. The major safety concerns relate to the central nervous system depressant effects of overdose, addiction and arrhythmias.

DPP is available in two forms. The hydrochloride salt is more soluble and more rapidly absorbed, resulting in high plasma concentrations in overdose. As such, it is more likely to be abused. This form of DPP can even be dissolved and main-lined. Lentogesic® is a hydrochloride salt. The napsylate salt (e.g. Synap Forte®) is less soluble and less rapidly absorbed, making it unpopular with addicts. From an abuse and overdose perspective, the two salts behave almost like different drugs. A dose of 65 mg of the hydrochloride salt is as efficacious as 100 mg of the napsylate compound.

DPP is metabolised by the cytochrome P450 enzyme system (CYP3A4) to norpropoxyphene, which is pharmacologically active and has a half-life of up to 30 hours. This compound is allegedly associated with QT prolongation and potentially fatal dysrhythmias. Once again, the hydrochloride salt may produce higher peak norpropoxyphene levels, with greater potential for complications.

Efficacy data for all weak analgesics are confounded by different pain models (e.g. third molar extraction, bunionectomy), the placebo effect, the comparison of inadequate doses of one drug with full doses of another, the comparison of different formulations and additives, and inter- and intra-patient variation in pain reporting.

Some observations regarding DPP efficacy:

- One and a quarter Synap Forte® tablets, equivalent to 65 mg of DPP and 650 mg of paracetamol, produces equal analgesia to 100 mg of tramadol, but is better

tolerated from a gastrointestinal perspective.

- When comparing the weak opioid-paracetamol combinations, the rate and severity of adverse drug reactions were significantly higher with tramadol combinations than with DPP combinations (with the exception of liver enzyme elevation), but lower with codeine combinations at a 10 mg, but not 30 mg, dose of codeine.
- As a single agent, neither DPP, nor other weak oral opioids, performs better than full-dose paracetamol.

There are two main safety concerns: toxicity in overdose situations and toxicity at normal therapeutic doses. South African data reveal that DPP is very infrequently associated with suicides or accidental overdose: 0.6% of overdoses have implicated DPP; 0.4%, tramadol; 27%, paracetamol; 13%, antihistamines; 14%, NSAIDs; and 15%, amitriptyline. This reflects local scheduling and availability of the respective drugs. The OTC availability of DPP hydrochloride in the UK made it a far more likely drug of abuse in that country.

Overdose of DPP is associated with cardiovascular collapse. Adverse cardiac events include bradycardia, asystole, bundle-branch block, non-specific QRS broadening, QT prolongation, reduced myocardial contractility, peripheral vasodilatation and hypotension. Cardiac abnormalities are not universally present in cases of overdose, and central nervous system and respiratory depression may be frequent causes of demise, as would be expected with opioid overdose. One case report of torsades de pointes exists related to normal therapeutic dosing of DPP. The mechanism of conduction abnormalities relates to the blockade of sodium channels (i.e. powerful blockade and slow dissociation lead to QRS widening, complete heart block and prolonged ventricular tachycardia), and the delayed potassium rectifier current (i.e. prolonged repolarisation leads to prolonged QT and potential for torsades de pointes). Treatment includes hypertonic saline and intravenous lignocaine.

So, is cardiac toxicity a concern at real-world, South African dosages? The major factor leading to the worldwide withdrawal of DPP has been the findings of the FDA Mandated Multiple Ascending Doses (MAD) study. This study examined the impact of different doses of DPP on PR, QRS and QT durations and intervals in healthy volunteers, as well as the plasma levels of DPP and norpropoxyphene that were achieved. For 11 days, six patients in each group received either placebo, 600 mg of DPP napsylate per day, 600 mg of DPP napsylate plus (extraordinarily) some DPP-containing placebo per day, or 900 mg of DPP napsylate. Serial 12-lead electrocardiograms and plasma analyses were done.

It has been observed that a 20 millisecond prolongation in QTc is associated with a statistically increased risk of dysrhythmias. MAD found that:

- Increasing doses of DPP produced exponentially increasing plasma levels of DPP and norpropoxyphene. Doses of 900 mg/day resulted in plasma levels that were 2–2.6 times higher than those observed at doses of 600 mg.
- The 600 mg dose produced a mean QTc prolongation of 17 milliseconds. This is below the risk threshold, but the upper confidence limit of 21.8 milliseconds fell within the risk category. It should be noted that the two 600 mg groups were analysed together, despite the fact that half of the patients actually received more than 600 mg/day. Clearly a study that would not have withstood peer review on this count. The 900 mg dose resulted in a mean QTc prolongation of 27.9 milliseconds. DPP can, therefore, be described as having a narrow therapeutic window in terms of this complication
- It was felt that the highest doses equated to, or even underestimated, mathematically modelled plasma concentrations that were likely to be achieved only in extreme old age and liver and renal dysfunction.
- No deaths or serious adverse drug reactions were observed, but two patients in the high-dose group withdrew because of nausea and vomiting, malaise and restlessness.

The FDA concluded that these findings confirmed the phenomenon of QTc prolongation with DPP at these doses. This finding is not unique to DPP, but has been observed in a variety of drugs, including sotalol, dolasetron, chloroquine, saquinavir, tricyclic antidepressants and chemotherapeutic agents. In most of these instances, the therapeutic benefit was felt to outweigh the arrhythmic risk, regulatory registration was maintained, and suitable physician cautionaries were added to the packaging. These drugs were felt to be agents with low abuse or overdose potential. In the case of DPP, the net clinical benefit (analgesic effect vs risk) was considered insufficient to balance the abuse potential and proarrhythmic effect of the drug.

Some observations arising from these findings related to the use of DPP napsylate in the postoperative pain environment in South Africa:

- The doses tested were 50% higher than those registered for DPP napsylate in South Africa, and the plasma levels achieved after administration of registered formulations would likely be more than 50% lower, because of elimination kinetics.
- The duration of therapy was six days longer than the registered duration of therapy in South Africa.
- Dose adjustment, for extremes of health and age, is already recommended and practised by most anaesthesiologists.

Table I: Common combination analgesics and their components

	Paracetamol	Aspirin	NSAID	Weak opioid	Additives
Stopayne® Stilpane®	320 mg			Codeine 8 mg	Meprobamate
Myprodol® Mybulen®	250 mg 350 mg		Ibuprofen 200 mg	Codeine 10 mg	
Synap Forte®	500 mg			DPP napsylate 50 mg	Caffeine Diphenhydramine
Lentogesic®	400 mg			DPP HCl 65 mg	L - glutamine
Tramal®				Tramadol 50 mg	
Tramacet®	325 mg			Tramadol 37.5 mg	
Codis®		500 mg		Codeine 8 mg	
Betapyn® Syndol® Adco-Dol®	X			Codeine	Caffeine Doxylamine
Tenston®	X	X		Codeine	Caffeine Meprobamate
Distalgesic® Doxyphene	X			DPP (highest dose)	
Dolorol Forte® Painamol® Panado-Co® Empacod®	500 mg			Codeine 8 mg	
Doloxene®		X		DPP	
Suncodine®	X			Codeine	Caffeine Phenyltoloxamine

- Those with valid concerns about the potency of DPP (and, incidentally, codeine and tramadol) often fail to recognise that the drug is rarely used as a single agent, but rather as a component of multimodal analgesia. There is use in pointing out that DPP is only as potent as full-dose paracetamol or NSAIDs anyway, when we are already using full-dose paracetamol and NSAIDs and require further analgesic options.

### What is really in our combination analgesics?

There remain more combination analgesics on the South African market than anywhere else in the world. Some of the combinations are rational and aim to provide multimodal analgesia in a single pill, while others defy reason and could be regarded as frankly cynical, incorporating sedatives (barbiturates or antihistamines) and stimulants (like caffeine or l-glutamine), which all serve to increase the addictive potential. These agents have potential for abuse and are controlled by being given schedule 5 status. There certainly is a place for interrogating the relevant pharmaceutical companies regarding the rationale for the sedative and stimulant additives, and for lobbying for cleaner combination agents.

Some of the popular brands containing weak opioids and their constituents are shown in Table I.

### When should we not use DPP?

The current situation, with everyone awaiting the outcome of the appeal against the MCC's decision, allows the prescription and marketing of DPP-containing drugs. However, some clinic groups have already withdrawn all such agents from their pharmacies. The fact that a gradual withdrawal was ordered prior to the appeal indicates that there was some awareness of the number of patients receiving these drugs and of their pivotal place in pain management, and that the adverse effect triggering the withdrawal is not considered critically urgent.

We need to differentiate between agents. Synap Forte® is a safer formulation (in terms of dose and DPP salt) than Lentogesic®. Distalgesic®, on the other hand, allows dosing up to the FDA toxic threshold.

We also need to think about the combination drugs and their constituents before prescribing, and individualise our approach based on patient history, demographic and disease factors and nature of surgery. There is no doubt that one combination agent is easier to use than three or four single agents. However, as far as combinations go, we need to exert pressure to rid these agents of undesired additives.

If we elect to utilise DPP-containing drugs, we should:

- Prescribe appropriate, standard doses, and for as short a time as is appropriate.

- Explain to our patients that we are using the drug based on sound scientific principles: at a safe dose and for a safe duration. They should also be told that they should discontinue the agent should they develop unwanted symptoms.
- Avoid co-prescription with other central nervous system depressants, and warn patients to not to ingest alcohol.
- Avoid DPP-containing drugs in depressed and suicidal patients.
- Avoid DPP-containing drugs in patients with cardiac disease or known conduction abnormalities.
- Avoid co-prescription with drugs known to prolong the QTc, such as tricyclics, antiretrovirals, antiarrhythmics and chemotherapeutic agents.
- Practice significant dose adjustment in the elderly and patients with impaired hepatic, cardiac or renal function. In the most frail patients, the dose prescribed should be reduced to 25% of recommended dose.

### Is only DPP potentially dangerous?

Sick, frail, concurrently medicated, very old, very young, organ-impaired and pharmacogenetically outlying patients develop complications or unexpected reactions after administration of a variety of drugs. An exhaustive list of the potential problems associated with other weak opioids, paracetamol and NSAIDs is beyond the scope of this editorial. We are all aware of the toxic potential of paracetamol in moderate-to-severe hepatocellular disease and liver resection surgery. The gastrointestinal, renal, cardiovascular and haematological effects of NSAIDs are also common cause for concern, and the other weak opioids are discussed below.

#### Codeine

Codeine is a pro-drug, and subject to wide pharmacogenetic variation in its conversion to morphine by CYP2D6. Up to 25% of the population are either slow metabolisers (little clinical effect is achieved) or ultra-metabolisers (profound oversensitivity to the agent). A good history should identify such patients, unless they are pharmacologically naïve.

Codeine is not recommended for analgesia after rectal surgery, especially haemorrhoidectomy, because of the high risk of constipation.

#### Tramadol

Tramadol is associated with a significant risk of nausea and vomiting (i.e. serotonergic effect), and there are concerns about the antiemetic efficacy of some 5-HT<sub>3</sub> inhibitors and the analgesic efficacy of tramadol when these drugs are used in combination. Tramadol is contraindicated in the presence of other serotonergic drugs, e.g. selective serotonin and

noradrenaline reuptake inhibitors (SSRIs and SNRIs), because of the risk of serotonin syndrome. So, if our patient is a young female, scheduled for haemorrhoidectomy, on an SSRI with a previous history of postoperative nausea and vomiting, a peptic ulcer and a family history suggesting she is a CYP2D6 ultra-metaboliser, what should we do?

### Conclusion

There is no doubt that DPP, like aspirin, paracetamol and NSAIDs, is a toxic and potentially lethal drug. It may possibly produce QT prolongation at standard or modestly supratherapeutic doses. As far as efficacy goes, what we are looking for is not to find and use the strongest drug, but to be able to practice multimodality: using a number of different drugs at modest doses to target different components of pain.

We do need to think about what is in our drug combinations and what is appropriate for the particular patient and situation, and not merely to prescribe “knee-jerk analgesia”. Some combinations are frankly irrational. But we do need to have a range of drugs available from which to pick and choose. There are situations in which the two remaining weak opioid options not containing DPP are unsafe and even contraindicated. What are we to do then? We cannot abandon patients without effective home analgesia for fear of using a potentially dangerous drug.

As we stand at present, DPP-containing drugs can still be prescribed in South Africa, despite having been withdrawn in many other countries, in part on the basis of flawed science. Some hospital groups have withdrawn all DPP-containing drugs from their pharmacies as a precautionary measure. Several alternatives to DPP are available, but appropriate prescription, for each individual patient and clinical circumstance, should be encouraged. Current South African scheduling and packaging should continue, to ensure that Synap Forte® (at least) remains a safe and useful component of our analgesic armamentarium.

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