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Dose optimisation in pain control

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Abstract

The driving force in clinical dose optimisation for pain control is titration to effect. It is the pharmacodynamic dose to effect relationship rather than pharmacokinetic dose to concentration which has fostered particular recent intellectual interest. In part, this is because the relationships between plasma concentration and effect are perhaps more subtle in pain control than in some therapeutic areas, and in part because the (deceptively simple) therapeutic target is pain relief, rather than a particular blood pressure or hormonal level. Some 30 years ago, there was a simplistic attempt to define plasma concentrations at which opioids would be effective. In reality, the variability in the plasma concentration at which analgesia is achieved is colossal, not least in contexts where patients have previous opioid exposure. Perhaps the best that can be said about such approaches is that without any opioid in the body there will be no analgesia. The amount of drug required to produce analgesia is the amount necessary for the patient to report that the pain is controlled. This may be much greater with previous opioid exposure. © 2001 Elsevier Science B.V. All rights reserved.

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1. Conventional analgesics

1.1. Opioids—a principle: dose titration and differences between clinical and laboratory pharmacology

Opioid clinical use shows up a difference between clinical pharmacology and laboratory pharmacology. What happens when opioids are given to someone in pain is different from what happens when they are given to someone not in pain. The respiratory depression which haunts acute opioid use is seen readily in studies of volunteers who are

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not in pain. But respiratory depression is minimal when appropriate regular doses of opioid are given to patients in chronic pain. Patients maintained on oral morphine without respiratory depression who then receive successful nerve blocks must have their morphine dose reduced. Failure to reduce the dose will result in respiratory depression [1,2]. One explanation is that the respiratory centre receives nociceptive input [3]. Presence of this input counterbalances the respiratory depressant potential of the opioid. Absence of this pain input, for instance because of a successful nerve block, leaves the respiratory depressant effect of the opioid unopposed.

The clinical message is that opioids need to be titrated against opioid-sensitive pain. Excessive doses, doses bigger than needed to relieve pain or doses given when there is no pain, will cause respiratory depression. A postoperative patient still complaining of pain when the previous dose has had time to be absorbed needs more drug. This difference between opioid pharmacology in the presence and absence of pain also applies to addiction. The drug-seeking behaviour synonymous with street addiction is not found in patients after pain relief with opioids, not in childbirth, nor after operations nor after myocardial infarction [4]. Street addicts are not in pain. The political message is that medical use of opioids does not create street addicts, and restricting medical use hurts patients.

This principle, dose titration against effect, is illustrated in Fig. 1. The clinical skill is in prescribing an initial dose which is close to the necessary dose to relieve pain effectively, with subsequent repeat doses which keep the patient "below the line" above which adverse effects will cut in. We know that age, gender and race are relevant factors, and that weight is a poor guide [5]. The older, the female and black people on average require less opioid to achieve analgesia (Fig. 2). Whether this is kinetic or dynamic remains contentious.

1.2. Metabolism

Of all opioids, morphine is historically the first choice, and yet its metabolism has a major enigma directly relevant to dose titration. Morphine has an active metabolite,

Principle for Safe & Effective Opioid

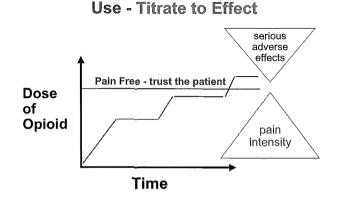


Fig. 1. Titrating opioids against effect.

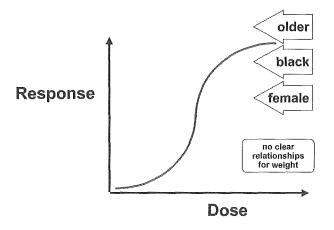


Fig. 2. Age, gender and race with opioid dose-response.

morphine-6-glucuronide (M6G), which is important because it is a major metabolite in man and because it is more potent than morphine. M6G was 10-20 times more potent intrathecally than morphine [6], and M6G may contribute to the analgesic effect of morphine, acting through a different receptor subtype [7]. In a systematic review of 56 kinetic studies with information on 1212 patients, the effect of age, renal impairment, route of administration, and method of analysis on the ratios of morphine-3-glucuronide to morphine (M3G/M) and morphine-6-glucuronide to morphine (M6G/M) and the M3G/M6G ratio were studied [8]. Across all studies, the range of the ratios of metabolites to morphine was wide (0.001–504 for M3G/M, and 0–97 for M6G/M).

Neonates produce morphine glucuronides at a lower rate than older children or adults. Metabolite ratios are higher in renal impairment. Routes of administration which avoid first pass metabolism (intravenous, transdermal, rectal, intramuscular, epidural and intrathecal) result in lower metabolite production than oral, buccal or sublingual. Metabolite production was similar for single and multiple dosing. There was no evidence of differences between method of assay. There was a high correlation between the two glucuronide metabolites in spite of the different situations studied, supporting a single glucuronidating enzyme. Morphine is present in CSF at a four-fold higher concentration than the glucuronide metabolites [8]. We still do not know how much of the analgesia from a given dose of morphine is produced by M6G, or indeed whether this is more important for oral use and in chronic dosing. What we do know is that in neonates and in patients with renal failure, we can expect greater analgesia from a given dose of morphine because of the higher M6G/M ratio.

1.3. Within route formulation impact on dose optimisation

When chronic pain is managed with morphine, the oral route is preferred. Titration to effect can also be complicated by use of different formulations. Clinically important issues include the potential interchangeability between formulations, the applicability of results

from healthy volunteer studies to patients, dosing intervals based on C_{max} and T_{max} and the question of the accumulation of morphine.

A systematic review used all available studies in patients and healthy volunteers to examine the C_{max} and T_{max} of different oral morphine formulations, and to clarify factors producing any underlying variability [9]. The first, and obvious, conclusion was that the C_{max} and T_{max} obtained with immediate release, controlled release and once-daily formulations differed in the expected manner, so that the respective T_{max} values were 1, 3 and 9 h.

A second clinically important point is that within formulation, there was little difference between different salts or different brands. For the immediate release formulations, there was no difference in either C_{max} or T_{max} between solution and tablets, or between different salts. Choice then comes down to cost and availability. Similarly, among the controlled release formulations little difference was seen for either C_{max} or T_{max} between MST Continus and the relatively sparse data for the other brands. Values for those other brands fell within the range observed with MST.

This work also supports previous observations that there is little evidence for accumulation with multiple dosing of morphine, because the C_{max} values for single and multiple dosing were not different.

The question of whether being fed or fasted alters morphine absorption was also addressed. No difference was found in C_{max} for fed and fasted healthy volunteers for either controlled release or once-daily formulations. Food also appeared to have little effect on the time taken to reach maximum concentration in controlled release formulations. However, fasted subjects appeared to reach maximum concentration around 2 h earlier than fed subjects when receiving once-daily formulations. The T_{max} results for once-daily formulations also appeared to show a difference between the two brands. The T_{max} value from the single trial of MXL was considerably lower (the lower outlier in both fed and fasted) than seen with Kapanol.

1.4. Pragmatic dose optimisation: oral morphine—success and failure

In chronic pain, opioids are usually given by mouth. The dose is worked out by titration to effect over a period of days, and then the drug is given regularly, not waiting for the pain to come back. Initial problems with nausea or dizziness commonly settle. If constipation is likely, laxatives are given. If patients' pain starts to increase, the dose is increased. Cancer pain audits report that using analgesics according to the WHO ladder can relieve pain for 80% of patients (but see Ref. [10]). For most of the 80%, the relief will be good; for a minority, it will only be moderate.

Oral opioids will 'fail' when patients cannot swallow, and then change of route, to sublingual, transdermal or suppository is necessary. The common reasons why oral morphine fails in patients who can swallow are intolerable or unmanageable adverse effects, opioid insensitive pain and movement-related pain. These situations present particular clinical problems for both diagnosis and management, and the controversy between advocates of change of drug or change of route (same drug) continues.

Intolerable or unmanageable adverse effects due to opioid action via opioid receptors will not logically be improved by changing to an equi-analgesic dose of a

different opioid which acts on the same receptors. For this to be true would require different dose-response curve slopes for effect and adverse effect for different opioids, and we have little evidence for such differences. The case reports of changing opioid to reduce the adverse effects and maintain analgesia often describe complex cases which defy simple interpretation, but there is a hint from a randomised study [11] that there may be exploitable differences. In that double-blind crossover, morphine and oxycodone hydrochloride were given to 20 severe cancer pain patients. Equal analgesia was achieved with both morphine and oxycodone, but morphine caused more nausea than oxycodone and hallucinations occurred only during morphine treatment. Whether changing route of administration (same drug) can improve the balance between efficacy and adverse effect is unclear. The necessary evidence would come from randomised comparison of oral and injected dosing with the same drug (see Ref. [11]).

1.5. Changing drug (opioid rotation) or changing route of administration

By now it should be clear that oral morphine is the standard oral opioid, and that the clinical dilemma when oral morphine does not work is whether to change oral opioid or to change the route of administration (Fig. 3). Like most dilemmas, the problem is that there is little quality evidence to guide the clinician. Those who can change route change route, those that cannot change drug. Until we have more hard evidence that there is genuine advantage in changing drug, such as differential adverse effect incidence, or evidence from a randomised comparison of the two strategies, the controversy will continue to simmer. A small randomised study showed that changing from oral morphine to subcutaneous or epidural morphine improved pain relief and reduced adverse effects [12]. Until there is a credible randomised trial of adequate size, we can all continue with our beliefs unchallenged. My vote is to change route not drug, but I am in the privileged position of being able to do this.

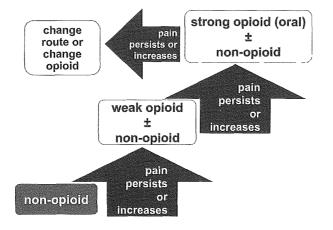


Fig. 3. WHO analgesic ladder for cancer pain management amended with a 'fourth' stage to show the dilemma about change of route or change of drug when oral morphine fails.

There are further levels of difficulty. When changing between drugs (same route), comparisons must be made at equi-analgesic doses. When changing between routes of administration (same drug), the dose of the drug must be adjusted, particularly between oral and parenteral routes if the opioid undergoes extensive first pass metabolism. Endless argument can result. For morphine, the effect of a single injected dose was six times that of a single oral dose [13]. In the multiple dosing context of chronic pain, ratios of 2:1 or 3:1 are used successfully. The active metabolite may contribute more to the analgesic effect with repeated doses than with a single dose [8]. The third level of difficulty is that goalposts move. The original spinal (generic for intrathecal and extradural) opioid question was whether spinal opioid alone was better than simpler injection routes. Randomised comparison of subcutaneous and epidural morphine showed little difference [12] (other than reduced epidural dose) for efficacy and adverse effect. Now it is the use of spinal combinations of local anaesthetic and opioid which promises the greatest clinical benefit.

Continuous spinal infusions of a combination of local anaesthetic and opioid exploit the synergy between local anaesthetic and opioid [14,15]. Low doses of both components can provide analgesia with little loss of mobility. While there are many randomised trials of these combinations in postoperative pain, there are few in chronic pain [16]. Such spinal infusions can succeed in neuropathic and movement-related pain when oral opioid has failed, and adding clonidine may provide additional benefit in neuropathic pain [17]. Technical debate continues over the relative advantages of epidural versus intrathecal and high cost implant versus simple percutaneous catheters and external syringe drivers. For us, the low-tech epidural with external syringe driver works well.

1.6. Enigmas-tolerance

Tolerance is the need for a bigger dose (or higher plasma concentration) to achieve the same pharmacological effect. Clinicians argue that the need for a bigger dose is driven by worsening disease rather than by pharmacological tolerance, and cite the fact that patients are often maintained satisfactorily on the same oral morphine dosage for months. It is ingenuous to argue that opioid tolerance does not occur in man. Two classic experiments showed chronic tolerance when patients' analgesic response to a test dose was measured before and after chronic dosing. In 10 patients 'challenged' with a single dose of morphine, before and after 2 weeks of regular morphine injections, the response to the second challenge was less than to the first [18]. In 13 patients 'challenged' with single doses of either morphine or metopon, before and after 1 week of regular injections of either drug, again the dose-response curve was shifted to the right after the regular injections [19]. To complicate matters the change was greater for the drug which was given repeatedly after the first challenge (Fig. 4). The two studies show tolerance, less effect from the same dose after repeated injections, and, because the slopes of the four lines in Fig. 4 are different, incomplete cross-tolerance is evident from the second study.

Thirteen patients had a controlled relative potency assay comparing morphine and metopon (now extinct) after 1 week regular dosing with either drug [19].

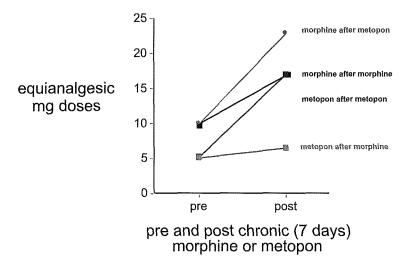


Fig. 4. Dose required to achieve same level of pain relief when rechallenged after 1 week chronic dosing [19].

The pragmatic issues are whether the dose escalation which some patients require and which produces difficult adverse effects can be avoided by changing opioid or route of administration, or by blocking tolerance.

2. NSAIDs and simple analgesics

Just as with opioids, it is titration to effect which is the guiding principle of dose optimisation. A complicating factor with NSAIDs is the relatively flat dose-response

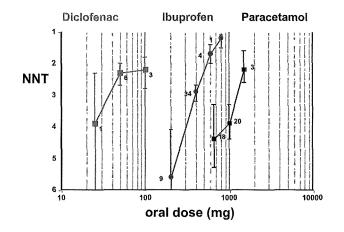


Fig. 5. Dose-response for oral ibuprofen, diclofenac and paracetamol for number-needed-to-treat (NNT-95% CI) to achieve at least 50% pain relief compared with placebo.

Ulcer bleed or perforation with aspirin

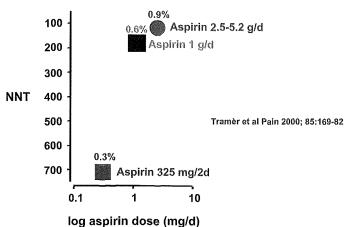


Fig. 6. Dose-response for ulcer bleed or perforation with aspirin.

curve for analgesic effect, seemingly as true for the coxibs as it is for their forerunners. It has been notoriously difficult to show dose-response curves for analgesic effect within individual trials, but the systematic review work shows that with data from thousands

Acute pain: at least 50% pain relief over 4-6 hours

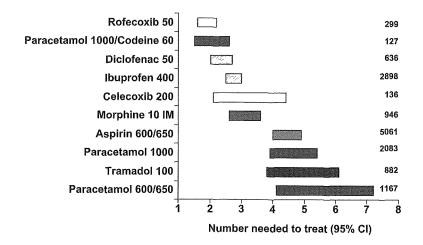


Fig. 7. Numbers-needed-to-treat to achieve at least 50% pain relief in postoperative pain.

rather than tens of patients the underlying dose-response curve for analgesic effect is revealed (Fig. 5) [20].

Perhaps this flat dose-response for efficacy is the reason so many clinicians are careless in stating NSAID dose. Also important in this is the realisation that the slope of the dose-response for adverse effects may be much steeper than that for efficacy. This point is brought home sharply with the gastrointestinal bleed data for aspirin (Fig. 6) [21].

While we have known for many years that oral NSAIDs could produce analgesia equivalent to that from (lowish) dose opioids, this point is reinforced by the league table of relative efficacy (Fig. 7).

We still have the intriguing question whether if we could increase the dose of NSAIDs safely we could produce greater efficacy than opioids. At present, the answer is clearly no.

3. Unconventional analgesics

Chronic cancer and non-cancer pain is not always relieved by opioids. Opioid insensitive pain may be defined as pain which does not respond progressively to increasing opioid dose. The commonest causes of opioid insensitive pain are nerve compression and nerve destruction. Controversy centres on whether the opioid insensitivity is absolute or relative. If it is relative (dose-response curve shifted to the right), then giving bigger doses would produce analgesia. The academic answer is that it is usually relative, but with the clinical problem that increasing the opioid dose provokes intolerable or unmanageable adverse effects. A working rule is that if the pain is in a numb area, as a marker for a damaged nervous system, we should be less confident that opioids will work except at doses which give troublesome adverse effects, and our threshold for considering other strategies (change of route or change of drug) should be lower. We have no simple way to test for opioid sensitivity other than time-consuming titration.

The usual pharmacological solutions for neuropathic pain include oral antidepressants, anticonvulsants and local anaesthetics [22], with spinal infusions of local anaesthetic and opioid mixtures as the last resort. There is still no quality evidence that changing from oral morphine to another oral opioid, methadone or ketabemidone, with different opioid receptor binding profiles, makes a difference. Differences in opioid sensitivity need to be considered in efficacy comparisons of changing opioid or changing route in chronic pain. The same drug by a different route must act on the same receptors. The issue is whether changing route allows dose increase and effective analgesia without increase in adverse effects.

3.1. Movement-related pain

Movement-related pain is, like neuropathic pain, sometimes very difficult to manage. Doses of oral opioid adequate to control the movement-related pain may be excessive when the pain stops (no movement). Two audits [23,24] show that pain on movement remains a major problem for half of those whose pain is controlled at rest. Fast-onset fastoffset opioids by injectable routes might improve management of pain on movement.

3.2. Antidepressants and anticonvulsants

The evidence that anticonvulsants and antidepressants are effective analgesics in neuropathic pain syndromes is quite strong. One of the many interesting twists is that the two drug classes appear equally effective, with the clinical choice determined by adverse effect incidence, for which we have less compelling data. In the two clinical marker syndromes, diabetic neuropathy and postherpetic neuralgia this equivalence of the two drug classes is marked [25]. This judgment is bedevilled by the question of the adequacy of dose optimisation. Therapeutic drug monitoring is rarely used in this context, with dose determined by clinical effect and adverse effect. We know that we can show dose–response relationships and we are confident that these are analgesic rather than mood effects. What we do not have is good trial data comparing one antidepressant or anticonvulsant with another, or indeed head-to-head comparisons of antidepressant with anticonvulsant.

4. Conclusion

For both conventional and unconventional analgesics, dose optimisation is based on dose to effect rather than by reference to plasma concentration. This conceals a number of puzzles, from the role of M6G in morphine analgesia to the flat dose–response efficacy curve for NSAIDs.

Appendix A. Discussion 9

L. Sheiner: About your last remark, let me say that unsubtle and unthinking PK/PD approaches will of course be useless. I don't think anyone here doubts that. I would suggest that the more complicated is the PK/PD relationship, and the more factors that enter into it, the more important it is to be explicit about them and the more useful it will be to get them quantitatively correct. That is to say, to the extent that models are useful, they may be correspondingly more difficult to construct. As an example, consider again the dose response for ketorolac: it becomes a lot easier to understand the data when the drop-out is dealt with properly, as it is in the model we used. Last observation carried forward, which is an improper (but simple) way of dealing with dropout, turns out to obscure the real dose response, not clarify it. I wanted also to say that I like the idea of having the standard by which we compare doses or drugs be something like your reciprocal probability of having 50% pain relief in 46 h. This is exactly the kind of thing we should be basing doses on. I would point out also that it is a derived quantity; that is, it's not directly observable. So some kind of modelling, whether it's just drawing a picture and a line through it, is required to generate that number and my feeling is if some kind of modelling is needed why not do the best kind you can?

P. Joubert: Analgesia is an area which is strongly influenced by placebo responses and placebo-type therapies. I just wondered if you know of any data about the influence of the

first dose, for example the lack or the presence of a response for the first dose, on the response to the second dose?

H. McQuay: I don't think analgesia is any more bedevilled. In fact less bedevilled perhaps than antidepressant studies and many other areas of medicine, including even, suprisingly perhaps, anti-emetics, but certainly, migraine and others. There is very little on repeat placebo usage: there's a lovely Italian study which probably would not get institutional review board consent now, which was to take a cohort of women who had dysmenorrhea, and for each successive menstrual cycle they were given tablets A, B and C. But one particular sub-group had placebo on repeated cycles, and the placebo effect waned as time went by.

G. Levy: There is an early paper published in the New England Journal of Medicine, in which patients received as a first dose either a placebo or an effective drug. Then the second dose effect was measured, and the second dose was always the active drug. Patients who had received a placebo as a first dose did not respond as well as did patients who received an effective dose, or a dose of an effective drug, which illustrates that expectations seem to be very important in the response to an analgesic agent.

H. McQuay: I think that's the same with the Italian women with the painful periods. In the end they got fed up and threw the pills away, because they didn't work anymore. Placebo effect wanes.

A. Breckenridge: Now that we're in the era of patient-controlled analgesia (PCA), how do the data on dose–response relationships cope with traditional type of data which you've been showing?

H. McQuay: One of the huge disappointments has been the complete inutility of the PCA data in research terms. Largely as a function of the fact that the protocols by and large have been academic-generated rather than industry-generated, therefore, the studies are of very poor quality, and second, the numbers have been very small. The variability on the PCA response is huge, and the classic academic way of doing it is, "I'll have 30 patients per group and lob it in", and you get nothing sensible out. And then we have the side issue of the opioid sparing effect, that is that the PCA requirement overall would decrease if you made some other analgesic intervention. And again, virtually all those studies were bedevilled by poor quality, poor organisation and are just not credible enough. I can remember talking with people like Ray Houde and Lou Lasagna in the early 1980s, where we all thought that PCA would answer and sort out some of our intellectual problems here about the mechanisms, but that has just not proved to be the case. As a study sponsor with limited budget I think you would be crazy to go in using PCA as the outcome measure unless you had a huge numbers and simple protocol sort of study. Because we know that the variability is enormous.

S. Erill: I just want to report that in 1954, Lou Lasagna published a paper in which he studied the effects of placebo for 21 days in patients with tuberculosis. He was measuring appetite and well-being, and there was a build-up effect.

X. Carné: If I correctly understood, you said that the dose-curve relationship in efficacy and toxicity for non-steroidals anti-inflammatory drugs is flatter. I completely agree with that. We performed a big epidemiological study on upper gastro-intestinal bleeding at the beginning of the 1990s, and we saw many cases that were using piroxicam behind 20 mg, but never 10 mg per day. The best predictor on gastro-

intestinal bleeding for non-steroidal is age. It's very rare to see an upper gastro-intestinal bleeding of people younger than 40 years old. I think that dose—response relationships are not equal in efficacy and in tolerability and both must be taken into account, and I think that in that epidemiological sense it's very important to understand things how are they doing.

A. Breckenridge: Can I come back to the question I asked Lew Sheiner after his talk, and put the question to Pedro and to Henry, about our ability to predict safe and effective doses in children in anaesthesia and analgesia?

P. Gambús: There has been some work done in anaesthesia in paediatric population as far as I remember at least with propofol, and also with alfentanil to be used as an analgesic. Usually when you need to do such a study, you have the constraints of the ethical committees, because you can not draw that many samples. It's hard to get permission from the persons responsible for the kids, so that can explain to some extent why there is this lack of models available for this population.

H. McQuay: There is remarkably little difference between the children and the adults in the analgesic world, apart from the neonate, differences in metabolic handling. I mean, you get the feeling that people are making careers unnecessarily out of this. The same principles apply just at sawn-off dose.

G. Levy: We've discussed dose optimisation, and we can't avoid inter-subject variability. Yet we haven't really addressed it in particular detail. I'd like to ask, what is your feeling about the likelihood of defining adequately certain co-variants that might help us predict the effective concentration, let's leave pharmacokinetics alone for a moment, the effective concentration of a drug in individual patients?

H. McQuay: Mainly there are three factors: age, gender and race.

G. Levy: That's what worries me in a typical clinical study. I think the studies are designed to fail, because they typically record, age, gender, smoking status, race, and renal function. I don't believe that has been very productive, and I think that there are a battery of other potential tests that can be used to characterise individuals, provided that they have a chance of being effective. My question is, where are we in terms of finding predictors, of efficacy or the necessary concentration of a drug? That we don't waste 6 months before we find the right dose or dose combination, treating hypertension or any other disease. Because all the modelling has certainly some general benefit in terms of helping logical thinking, but in the management of the individual patient, they're not sufficient or adequate. We have to find some others measures that tell us whether this patient needs large or small doses. In case of opioids, certainly the previous exposure to opioids is very predictive and so on, but other than that, where are we in the face of this very, very large inter-individual difference in effective concentration.

W. Evans: We are in early stages in several areas, one of which is the whole pharmacogenomics component of determining who's going to respond and who's not, or how they're going to respond to a given drug. And that field of pharmacogenetics has focussed largely on drug metabolism for a long time, but there's an increasing, rapidly growing body of data on polymorphisms in genes, encoding receptors or targets of drugs. And several of those have now been linked to drug behaviour in man. The beta receptor polymorphism, and albuterol response in asthmatic patients is one example. There's just a completely different response curve. One can see building that into the models, like Lew

was talking about, in terms of you would expect at the outset that the shape of the curve's going to be different for individuals who have inherited a different β -receptor than those who have a wild type receptor. It's going to get more complex because most drugs effects are polygenic, they're not monogenic in nature. But I think the tools are at hand to begin to elucidate those, and there was an interesting paper in the Lancet, early this year, that looked at it—it took a candidate gene approach for predicting who among a schizophrenic population being treated with clozapine was going to be successfully treated. They looked at known polymorphisms in serotonin receptors or transporters, histamine receptors, etc., and the model boiled down to six polymorphisms in three or four of those genes and had a 75% positive predictive power in that population. It was a Lancet letter, from a small group of individuals, but I think that's the kind of strategy we are going to see taken to try and bring the human genome data to the table in terms of predicting response to different kinds of medication.

N. Holford: If I can just come back to the issue of paediatric analgesia, I've been fortunate to work with Brian Anderson, who is a paediatric anaesthetist in Auckland who has studied several hundred children with ages ranging from neonates to young adults. He attempts to support the hypothesis that children are just small adults, which is the converse of the usual dogma that children are not small adults. In his work with paracetamol and other agents used in anaesthesia, he demonstrated that from a clinical pharmacology perspective children are indeed small adults. This is based upon scaling of pharmacokinetic factors (intra-species allometric scaling) and, at least with paracetamol, not being able to find any difference in the concentration effect relationship for the drug. One difference is in the time course of pain resolution after tonsillectomy, where children appear to recover more quickly than adults. With that exception, children are small adults for analgesia.

G. Levy: I agree with you provided that you exclude the neonate. The neonate is a very special system, that we know very little about and that's troublesome. Of course, paediatric clinical pharmacologists always invoke the developmental aspects, which we won't know about for the following 10 years. There are oestrogen exposure and all that. Basically, as far as I know, there has not been anything profound that the 2-, 3-years-olds represent. They are generally rapid drug metabolisers, and often somewhat larger doses are needed than in older individuals.

N. Holford: Brian Anderson has studied specifically the neonate (Anderson, B.J., Woolard, G., Holford, N.H.G. A model for size and age changes in the pharmacokinetics of paracetamol in neonates, infants and children. Br. J. Clin. Pharmacol. 2000; 50:125–134) modelling the changes in volume of distribution and clearance of paracetamol, which is pretty predictable, with a simple exponential change in volume of distribution and a half-life of about a week and for clearance of a half-life of just over a month. And then after 3 months, children become small adults for the pharmacokinetics of paracetamol. Similar patterns probably apply to other drugs.

W. Evans. In terms of cancer chemotherapy, children are not little adults. The reason is more than just metabolism differences. I agree with you that there are some clear data on the neonate and the young child having faster clearances. But the bigger issue in cancer is that it's a different spectrum of diseases. Children have different tumours than adults, so the dynamic side of the equation changes a lot. Even when they have the same diseases at

the cellular level in adults and children, actually at the molecular level they are quite different diseases. The spectrum of leukaemia seen in children is guite different, fortunately easier to cure than leukaemia in adults, because the adults have all the bad types of molecular fusions compared to the children. Part of the problem is that medications aren't being developed for kids, or at least for their tumours; they are being developed for the big markets, for the adult tumours. A drug company develops a drug for lung, breast or uterine cancer, so they can sell hundreds of thousand of doses, whereas any given type of childhood cancer, there are only a few thousand cases a year, so there is no market there. What we are left with is taking those drugs developed for breast cancer and trying to see if they'll work in a neuroblastoma, skeletal muscle tumour (rabdomyosacoma) or childhood leukaemia. It's been interesting because the experience was that the maximum tolerated dosage of most these drugs has turned out to be higher for children than adults, adjusted to body surface area and body weight. And so what was happening, maybe a decade ago, was there was a lot of time being wasted in phase I trials in children, giving very low doses that were homeopathic doses and with cohorts of three children going into each dose level, it took sometimes 10, 20 dose levels to get to an effective dose. The model changed, and the design was: start with, 80% of the maximum tolerated dose for adults, let that be your first dose level in children, since it usually takes more a hundred per cent anyway to see an effect. That's improved the process, it's made it a bit more efficient in terms of drug development in children. That's being related in part to their greater tolerance for the adverse effects than adults, and potentially differences in some cases of metabolism, they have to get a higher dose just to get the same exposure compared to adults. So the model shifted to something that's a bit more efficient, but it's certainly not perfect.

P. Joubert: Something that we have to deal with is the growth of genetics and genomics. If you have a polymorphism, how are you going to handle it as a drug developer out there? Would you potentially say everybody has to be genotyped or phenotyped? Are you going to individualise dosage? You could, for instance suggest that everybody should be treated as a fast metaboliser, so you overtreat and then backtrack on the adverse events emerging in slow metabolisers. Conversely, you treat everybody as a slow metaboliser and increase the dose in the non-responders. It again depends on the risk-benefit ratio and the nature of the adverse events and the rapidity you need to get a response. The example I often quote is the tuberculosis. In 3rd world settings where there is no money to do phenotyping in patients that get isoniazid you treat them all with a big effective dose for tuberculosis. If they are slow metabolisers and they start getting neuro-toxicity, you reduce the dose and/or you give them vitamin B supplements.

G. Levy: Lew Sheiner didn't emphasise in his presentation the fact that he used an entirely new approach to managing analgesiometric data. The visual analogue scale and other such measurements really don't lend themselves to any kind of data manipulation, since we do not know whether a scale value of 40 mm is twice as much pain as 20 mm. So this looking at probability is a fresh approach. On the other hand, I'm concerned whether people have gotten used to the kind of data presentation that derives from this kind of analysis; everybody is so used to looking at concentration versus time data and effect versus time data, that to look at probability versus time data takes a little bit of mental adjustment. One problem with analgesics is the stationarity of the system; even with

NSAIDs we've shown a fairly rapid development of tolerance. Also, prior experience dictates the response to subsequent doses. All these aspects are complexities that have to be faced. Meindert Danhof's presentation shows how valuable animal studies are, particularly from a mechanistic point of view, which is very important. But the other thing that has pleasantly surprised me over the years is the good correlation between effective concentrations in various experimental animals and in humans as long as you correct for protein binding and for the possibility of inter-species differences in some active or interactive metabolite. I wish that industrial experience in this area would be more widely made available in the literature because I think there are a lot of data in industry and we're going to have to find out whether this good correlation is largely limited to CNS-active compounds or whether it's also applicable to others. I know that in the case of the anti-coagulant effect of warfarin there's a good correlation in effective concentrations, once you make the appropriate correction for protein binding. Who knows how widely this correlation occurs? Listening to Pedro Gambús, I again was reminded of the ultimate dream of pharmacotherapy, namely real automated feedback control. If and when that comes about it's going to start in anaesthesiology. And the fact is that the difficulties have been very pronounced and progress has been slow, and that's also true, maybe for other reasons, for insulin administration; the glucose monitoring feedback control can be done nowadays but you need very large equipment to do that. But much of that progress will come, I think, in the area of anaesthesiology. With respect to pain control, at least in the United States, the issue of inadequate pain control has become a national scandal, which has been dealt with on a very high level now. AMA, NIH and others have tried to educate physicians, that there are patients who do need one or one and half or even two grams of morphine, while others will be killed by those doses. And there is still the notion of starting with a fixed regimen and then we'll look at the patient the next day and we'll see if the dose is adequate, that's clearly not appropriate. If there ever is a need for rapid determination of the optimum individualised dose, it is in the area of analgesia, where we are far, far behind.

A. Breckenrigde: I would like to reflect with you on what we've achieved over the last two and a half days. Let me say first that we didn't set this meeting up to discuss only warfarin. As Gary Levy said to me a couple of nights ago, you could teach the whole of a pharmacology course on warfarin, and I'd agree with that. I think we've highlighted several things. Firstly, I think we've shown those areas where there are real gaps in our understanding, and I would exemplify this by Terry Blaschke's talk this afternoon, where he showed quite clearly, the disappointment which he felt that the area of liver disease and optimal drug dosing which hasn't moved forward since he and several other people were active in the field several years ago. But I think we have identified several positive trends, and I'd just like to go through them. From several of the talks, imaging comes over as really a very powerful tool, and that's in spite of Nick Holford's negative comment this morning. It does seem to me that this is showing much promise, and quite clearly a lot of effort's going into it from industry. Undoubtedly the most powerful tool remains molecular biology, but we haven't yet fully released the value of this discipline in optimising dosing. Further I've learnt, that intensive investigation in certain disease groups pays dividends, and if one looks to what Bill Evans and Mary Relling told us vesterday about how working with relatively inadequate tools, one can, with imaginative application, work wonders in

therapeutics, and of course, optimal dosing is part of that. I think most of us are relatively comfortable with the status of our understanding of P450 and PK/PD modelling. Both these have definitely come of age, and I complement Pedro Gambús on his paper, a couple of days ago, showing how PK/PD modelling is being used in that hotbed of clinical pharmacology, the anaesthetic room. That was very impressive. TDM is probably not as important as its proponents would make out. Coming back right to the beginning of the meeting, discussing the pre-clinical leap, I thought that Kevin Park summarised it beautifully, by saying that each drug must be assessed on its own pharmacological and toxicological merits.

G. Levy: I can't let this meeting go by without reminding you of the beneficial role of animal studies. Meindert has already shown examples where the effect of concentration, whether you call it IC_{50} or whatever, of unbound drug in the plasma of animals is often very close to that in humans. Now when Terry spoke about the problems in liver disease, it reminded me of a study that we did that was initiated because of the many reports of falls and hip fractures in people with liver disease who were taking benzodiazepines. We initiated a study using either loss of righting reflex or rotorod performance in rats, and without any problem demonstrated a profound effect of experimental liver disease on the sensitivity to benzodiazepines. In about 15 years of studying the effect of disease on drug action, invariably when there was a well-documented human study, in other words, where protein binding changes were taken into consideration and proper measurements of effect were performed, invariably we could duplicate that in animals. I would suggest that it is highly appropriate in the course of drug development to perform pharmacodynamic animal studies in disease states I can think of at least dozen different disease states that can be induced very simply, and in many cases, for example renal failure, one can use different methodologies to produce renal disease in order to exclude the possibility that it's a specific effect due to a particular way of inducing the disease. I just want to go on record here that this is something that can be a very powerful tool. Now I've heard colleagues in industry say "we don't want anything to do with this, because if we do see a disease effect, FDA will make us perform specific studies in people with that disease, and that'll hold things up". I suggest that it may often be possible to simply include a statement in the package inserts, saying that animal studies have shown such and such, and while it is not known whether that can be found in humans, nonetheless this will forewarn people, perhaps to start with lower doses or be ready to use higher doses, and be mentally prepared for pharmacodynamic as well as pharmacokinetic changes in particular disease state.

References

- G.W. Hanks, R.G. Twycross, J.W. Lloyd, Unexpected complication of successful nerve block, Anaesthesia 36 (1981) 37–39.
- [2] H.J. McQuay, Potential problems of using both opioids and local anaesthetic [letter], Br. J. Anaesth. 61 (1988) 121.
- [3] F.M. Borgbjerg, K. Nielsen, J. Franks, Experimental pain stimulates respiration and attenuates morphineinduced respiratory depression: a controlled study in human volunteers, Pain 64 (1996) 123–128.
- [4] J. Porter, H. Jick, Addiction rate in patients treated with narcotics, N. Engl. J. Med. 302 (1980) 123.

- [5] R. Kaiko, Age and morphine analgesia in cancer patients with postoperative pain, Clin. Pharmacol. Ther. 28 (1980) 823-826.
- [6] A.F. Sullivan, H.J. McQuay, D. Bailey, A.H. Dickenson, The spinal antinociceptive actions of morphine metabolites morphine-6-glucuronide and normorphine in the rat, Brain Res. 482 (1989) 219-224.
- [7] G.C. Rossi, G.P. Brown, L. Leventhal, K. Yang, G.W. Pasternak, Novel receptor mechanisms for heroin and morphine-6 beta-glucuronide analgesia, Neurosci. Lett. 216 (1996) 1–4.
- [8] C.C. Faura, S.L. Collins, R.A. Moore, H.J. McQuay, Systematic review of factors affecting the ratios of morphine and its major metabolites, Pain 74 (1998) 43-53.
- [9] S.L. Collins, C.C. Faura, R.A. Moore, H.J. McQuay, Peak plasma concentrations after oral morphine-a systematic review, J. Pain Symptom Manage. 16 (1998) 388-402.
- [10] A.R. Jadad, G.P. Browman, The WHO analgesic ladder for cancer pain management, J. Am. Med. Assoc. 274 (1995) 1870–1873.
- [11] E. Kalso, A. Vainio, Morphine and oxycodone hydrochloride in the management of cancer pain, Clin. Pharmacol. Ther. 47 (5) (1990) 639-646.
- [12] E. Kalso, T. Heiskanen, M. Rantio, P.H. Rosenberg, A. Vainio, Epidural and subcutaneous morphine in the management of cancer pain: a double-blind cross-over study, Pain 67 (1996) 443-449.
- [13] R.W. Houde, S.L. Wallenstein, W.T. Beaver, Clinical measurement of pain, in: G. De Stevens (Ed.), Analgetics, Academic Press, New York, 1965, pp. 75–122.
- [14] T.J. Maves, G.F. Gebhart, Antinociceptive synergy between intrathecal morphine and lidocaine during visceral and somatic nociception in the rat, Anesthesiology 76 (1992) 91–99.
- [15] H. Fraser, V. Chapman, A. Dickenson, Spinal local anaesthetic actions on afferent evoked responses and wind-up of nociceptive neurones in the rat spinal cord: combination with morphine produces marked potentiation of nociception, Pain 49 (1992) 33-41.
- [16] H.J. McQuay, R.A. Moore, Local anaesthetics and epidurals, in: P.D. Wall, R. Melzack (Eds.), Textbook of Pain, 4th Edition, Livingstone, Edinburgh, 1999, pp. 1215–1231.
- [17] J.C. Eisenach, S. DuPen, M. Dubois, R. Miguel, D. Allin, Epidural clonidine analgesia for intractable cancer pain, The Epidural Clonidine Study Group, Pain 61 (1995) 391–399.
- [18] R.W. Houde, S.L. Wallenstein, W.T. Beaver, Evaluation of analgesics in patients with cancer pain, in: L. Lasagna (Ed.), International Encyclopedia of Pharmacology and Therapeutics, Pergamon, Oxford, 1966, pp. 59-98.
- [19] R.W. Houde, The analgesic connection: the Nathan B. Eddy memorial lecture, in: L.S. Harris (Ed.), Problems of Drug Dependence, NIDA Research Monograph 55 (1985) 4–13.
- [20] S.L. Collins, R.A. Moore, H.J. McQuay, P.J. Wiffen, Oral ibuprofen and diclofenac in postoperative pain: a quantitative systematic review, Eur. J. Pain 2 (1998) 285-291.
- [21] M.R. Tramèr, R.A. Moore, D.J.M. Reynolds, H.J. McQuay, Quantitative estimation of rare adverse events which follow a biological progression-a new model applied to chronic NSAID use, Pain 85 (2000) 169-182.
- [22] H.J. McQuay, R.A. Moore, An Evidence-Based Resource for Pain Relief, Oxford Univ. Press, Oxford, 1998.
- [23] R.K. Portenoy, N.A. Hagen, Breakthrough pain: definition, prevalence and characteristics, Pain 41 (1990) 273-281.
- [24] A. Banning, P. Sjøgren, H. Henriksen, Treatment outcome in a multidisciplinary cancer pain clinic, Pain 47 (1991) 129-134.
- [25] S.L. Collins, R.A. Moore, H.J. McQuay, P. Wiffen, Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review, Journal of Pain and Symptom Management, in press.