Dose response relationships in clinical pharmacology
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DOSE RESPONSE EFFECTS IN ANALGESIOMETRY: CLINICAL vs EXPERIMENTAL PAIN

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INTRODUCTION

If a patient complains of pain, the doctor asks about the nature of the pain, the history of the pain, precipitating and relieving factors, and about response of the pain to previous remedies. The clinical clues gained from that history are vital to sensible management. If the history leads to the diagnosis of trigeminal neuralgia then the appropriate prescription might be carbamazepine rather than narcotics. The converse would be true for postoperative pain. The doctor is aware that what is analgesic in one clinical setting is not necessarily so in another. The theme of this paper is that analgesic studies should take account of context in the same way as the doctor must do in the clinic.

It is not surprising that temporal and other factors are relevant in determining response to analgesics. Simple relationships between noxious stimulus and response, which have dominated laboratory investigation, are misleading, because it is increasingly apparent that the circuitry involved with nociception adapts to the stimulus. Receptive fields alter, firing patterns change, different neuro-transmitter systems become involved and oncogenic response is evident. Qualitatively and quantitatively these changes depend on the history, the context, of the noxious stimulus. The investigation of analgesic efficacy must then take account of context.

METHODOLOGY

There is still no objective measure of analgesia, but the methodology of subjective response measurement is surprisingly sensitive and reproducible. Successful use of these methods does, however, require that the investigators adhere to the rules which were defined by Beecher and refined subsequently [1,2]. If the rules are broken then anomalous results abound. One such was the finding that dihydrocodeine was not

an analgesic [3] in pain after oral surgery. A similar anomaly, critically important in discussion of dose-responses because of its widespread citation in the basic science literature, was the finding of a quantal rather than a graded dose response to intravenous morphine in postoperative oral surgery pain [4].

These two papers had postoperative oral surgery in common, but crucially they also shared a methodological flaw - both used elapsed time after surgery rather than pain intensity as the criterion for giving the test analgesic. Giving analgesics to patients who are not necessarily in pain does not augur well for the determination of dose response because there may be insufficient pain for the analgesic to show measurable effect. To break the rule that the pain should be the equivalent of moderate or severe on the categorical verbal pain intensity scale none, mild, moderate or severe is to risk such loss of sensitivity.

CONTEXT DEPENDENT ANALGESIA

Figure 1 illustrates a pragmatic definition of context for analgesic use, incorporating distinctions between duration of pain (acute vs. prolonged), sole analgesic or co-analgesic (administration with an analgesic known to work in that context) and nature of pain (somatic vs deafferentation).

The necessity for involving such definition of context is that classes of drug which are analgesic in, for instance, the sole analgesic/acute pain category are not necessarily analgesic in a prolonged

	Acute Pain	Chronic Pain
Sole Analgesic		nociceptive deafferentation
Co-Analgesic		nociceptive deafferentation

Figure 1 Defining the clinical context for analgesic effect

deafferentation pain. Arner and Meyerson have provided early controlled data for opiates in prolonged pain of nociceptive and deafferentation nature to support this distinction [5].

The importance of context definition for dose response to analgesics is that drugs which are analgesic in one context cannot necessarily be assumed to be so in another. Historically drugs effective as sole analgesics in acute pain have proved effective in chronic nociceptive pain, and this is valid for the range of conventional analgesics from aspirin through to morphine. The real problem comes in testing putative analgesics for the other contexts. One example is that the failure to demonstrate analgesic dose response for antidepressants as sole analgesics in acute pain was not predictive of co-analgesic efficacy [6], nor was it predictive for prolonged deafferentation pain, where antidepressants can be effective as the sole analgesic [7]. A negative result in acute pain as sole analgesic is therefore a likely predictor of lack of efficacy in prolonged nociceptive pain, but not for prolonged deafferentation pain.

CLINICAL - ACUTE PAIN

Dose and response

Opiates Many single dose studies have shown dose response to agonist opiates in acute pain. The example in Figure 2 is typical, and from such data slopes were derived for the determination of potency ratios. Such data came from crossover studies in postoperative pain, the commonest model until recently because of convenience, and the data has stood the test of time. Parallel group studies have recently superceded (numerically) crossover trials in postoperative pain because of the much shorter time that patients now spend in hospital after surgery.

Other than errors due to poor methodology mentioned above, confusion may arise with this 'classic' method when the comparison involves drugs (or the same drug) given by different routes, and the source of the confusion is the difference in the rate of absorption of the formulations. The oral to parenteral ratio for peak analgesic effect of morphine was determined as 1:6 in such a single dose crossover study [1]. The disparity between this result and the ratio of 1:2 or 1:3

used commonly in palliative care transition (multiple dosing) from parenteral to oral formulations has been the source of much controversy [8]. It is, however, explicable on the basis that the valid single

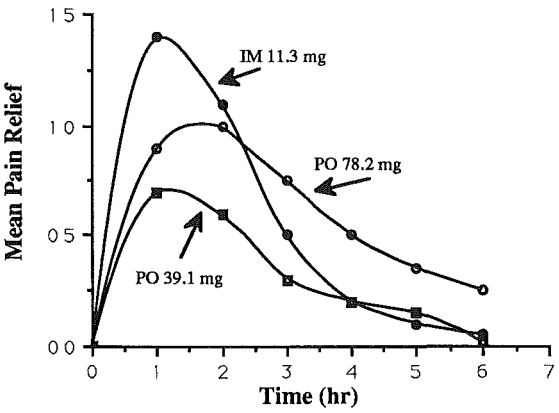

Figure 2 Dose-response curves for morphine by mouth and by injection (redrawn from Houde et al [1]

dose study downgrades the efficacy of the oral dose because of slow absorption compared with the intramuscular dose over the six hour study period, and because the clinical yardstick in palliative care is related more to total relief than to peak effect. The disparity highlights the fact that there are surprisingly few studies of multiple dosing, and these are necessary to answer clinically important issues.

Partial Agonists & Mixed Agonist-Antagonists Partial agonists and mixed agonist-antagonists have in general not shown the ceiling to analgesic effect expected from their pharmacology [9]. The explanation is presumably that within the normal therapeutic range the ceiling is not reached, and this has some support from evidence of ceiling to respiratory depression shown in the same clinical context as proportionate increase in analgesic efficacy [10]. The exception is nalbuphine; potency ratios obtained in different clinical contexts differed, and the ceiling was exposed as the severity of the pain increased. Laboratory pharmacology also predicts that use of agonist together with partial agonist or mixed agonist-antagonist will necessarily move the dose-response curve of the agonist to the right.

This is of great importance clinically, particularly because of sequential agonist / mixed agonist-antagonist use postoperatively and vice versa in chronic cancer pain. Within the normal clinical dose range there is little evidence for such dose-response curve shift [11,12]; the important caveat is that prior narcotic exposure can indeed produce such shifts [12].

Spinal administration of opiates Spinal administration of opiates (intrathecal and extradural) can produce extended duration of analgesia compared with conventional routes. The classic method of measuring analgesia (nurse observer collection of subjective response data) is logistically difficult if the analgesic under test is effective for much longer than 6 hours; the 12 (extradural) or 24 hours (intrathecal) duration of the spinal opiates highlight this problem. Cruder measures, such as the time to next analgesic or subsequent analgesic consumption, have however been sufficiently sensitive to show dose-response by these novel routes, and patient controlled analgesia has also proved effective.

Non-steroidal anti-inflammatory drugs Non-steroidal anti-inflammatory drugs (NSAIDs) have a special problem, which is the failure of higher doses to produce proportionate increase in analgesia as measured by peak or total analgesic effect in single dose studies. Such proportional increase in efficacy may be apparent if duration of effect is determined rather than peak effect, and survival analysis is one way by which this may be achieved. The explanation for the flat curves for peak effect may lie in the very real analgesic potency of these drugs, which have proved indistinguishable in oral formulation from parenteral opiates in a variety of clinical pains. An asymptote is reached on the dose-response curve if the doses given are more than adequate for the pain stimulus studied.

TABLE I EXPLANATIONS OF CEILINGS TO ANALGESIC EFFICACY

1. Study artefact: dose greater than required for pain stimulus (asymptote)
2. Intrinsic drug property
   partial agonist / mixed agonist-antagonist
   ? non-steroidal anti-inflammatory drugs
3. Efficacy limited by adverse drug reactions
   e.g. codeine, dihydrocodeine
   ? non-steroidal anti-inflammatory drugs

Patient controlled analgesia (PCA) PCA may be used to show dose-response to medication given before connection to PCA [10,13]. One major advantage of such study designs is logistic. If the study medication (given before connection to PCA) has a long duration of effect, such as 10 or 24 hours, the nurse observer measurement method may be inappropriate just because of the long study period. If a finer tool than the crude estimate of time to next analgesic is required, PCA is a real alternative. The disadvantage is that there are no studies providing validation of dose-response using PCA compared with the tried and tested nurse observer method. Within-patient the technique can be used to elicit a form of dose-response. By altering the concentration of drug delivered, the patient adjusts the rate of demand, in theory titrating to the same end-point as before the change in concentration. By changing the drug delivered by PCA equianalgesic dosage may also be determined within-patient, and such studies are in progress in the chronic pain setting [14].

Plasma concentration and response

Poor correlations between plasma opioid concentration and response have been the rule. The situation is confused by the lag between concentration change and change in effect [15]. This confusion is compounded when slow absorption rate routes are used. Again context is important. The concept of an absolute minimum effective plasma concentration of analgesic (analogous to minimum alveolar concentration for inhaled anaesthetics) is invalid in the absence of contextual

information, and yet paper after paper in the anaesthetic literature perpetuates this myth. The response of an opiate-naive patient given 10 mg of parenteral morphine is quite different from the response seen in a cancer pain patient who has been taking 500 mg of morphine daily for six months. Within-patient acute tolerance develops to a single dose of opiate. There was no difference in duration of analgesia between groups of patients given doses of fentanyl which differed by an order of magnitude [16]. The presence or absence of pain when the initial opiate dose was given may be a crucial determinant for the development of acute tolerance [17]. Whatever the mechanism, it makes a nonsense of the concept of a minimum effective concentration which fails to take context into account.

Convincing relationships between plasma concentration and analgesic effect for NSAIDs have not been conspicuous, perhaps because of the combination of flat dose-response curves (?common to all NSAIDs) and variability in plasma concentration [18].

Prolonged Clinical Pain - deafferentation (non-nociceptive) type

Anticonvulsants and antidepressants are used widely to treat shooting and burning deafferentation type pain respectively. The classic example is carbamazepine in trigeminal neuralgia. The absence of a clinical dose-response for analgesic effect with opiates is the most important principle in these pain conditions, and this may be quantified [5]. The fact that the absence of a dose-response for analgesic effect provides the operational distinction between opiate-sensitive (nociceptive) and opiate-insensitive (non-nociceptive) pains is of great clinical importance but also stresses that such dose-response relationships *do* hold in nociceptive pain. The reason why opiate sensitivity is lost is unknown. The simplest explanation, that absolute numbers of opiate receptors decrease following insult to the primary afferent fibres, appears untenable, at least in postherpetic neuralgia [19].

Unfortunately there is little evidence for graded dose-response for any of the various drug classes used in these pain conditions. The first priority is evidence of efficacy. While such evidence exists for anticonvulsants in trigeminal neuralgia or diabetic neuropathy,

and for antidepressants in postherpetic neuralgia or atypical facial pain, it is sadly lacking in many of the clinical settings in which these drugs are used. Given the lack of efficacy data it is not surprising that we lack the fine-tuning of dose-response evidence, but the real conundrum is whether or not these unconventional analgesics show a threshold or quantal effect rather than a graded dose-response. Clinical opinion appears divided, because two prescribing strategies exist. The first is to use these drugs as though a graded response existed, increasing the dose in the absence of effect until such point as effect or dose-limiting side-effects prevail. The second, the quantal approach, uses therapeutic failure of an empirically determined test dose as an indication to change drugs rather than to increase dose.

EXPERIMENTAL PAIN

Dose and response

For many years experimental pain was maligned as a predictor for clinical pain. The basis of this reputation was the failure of the major analgesic investigators to obtain sensitive and reproducible results, and this was true (and perhaps remains so) particularly of the ischaemic tourniquet test. Recent work with the other tests has been more rewarding, because sensitivity and precision have been achieved. Arguments as to whether or not the pain is 'similar' to clinical pain do not affect the pragmatic utility of a model which shows dose-response in a similar dose range to that used clinically. These recent results with experimental pain also obey the rule of context-dependence, because not all drug classes tested do produce analgesia in this context.

Figures 3 and 4 illustrate dose-response to opiates from two different experimental pain models, intravenous morphine in heat pain [20] and oral dipipanone in the cold pressor test [21]. Our own results support the efficacy of morphine in the cold pressor test [22]. The major enigma is the lack of efficacy of NSAIDs in experimental pain, indomethacin failing in a context where dipipanone was effective [23]

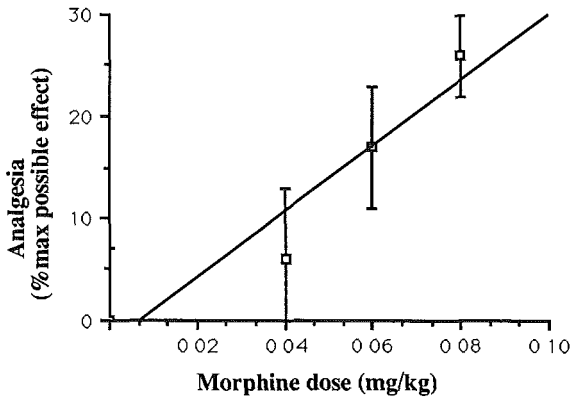

Figure 3 Dose-response for morphine in experimental (heat) pain (redrawn from Price et al [20])

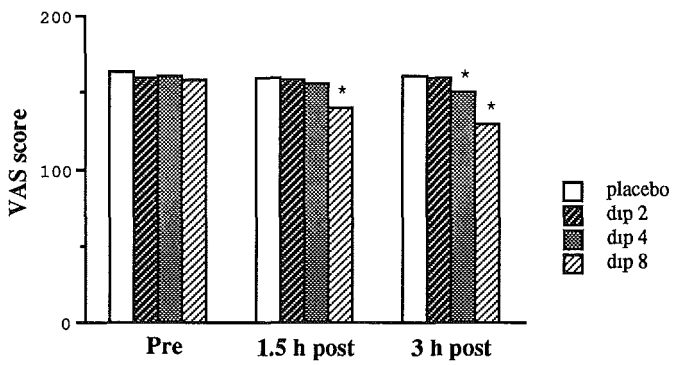

Figure 4 Dose response for dipipanone in cold pressor pain (redrawn from Posner et al [21]) dip=dipipanone, doses in mg, * = significant difference

and ibuprofen where morphine worked [22]. Using a 'noxious squeeze' stimulus distinction between aspirin and placebo has been achieved [24], but the result has yet to be repeated.

With centrally acting non-opiates and with antidepressants there is little compelling evidence for dose-response with experimental pain [25,26,27]. It seems especially ironic that the drug classes most difficult to test clinically, because of the heterogeneity of the pain conditions for which they are used, should also be the ones for which there is as yet no reliable experimental pain model.

Plasma concentration and response

A relationship between plasma concentration of morphine and analgesic effect has been shown on the cold-pressor model [22] using an oral morphine dose (Figure 5). No significant correlation was found over the three hour study period to plasma concentrations of the active metabolite morphine-6-glucuronide (M6G). This may reflect the short study duration compared with the time course of effect of the M6G. Relationships between plasma opiate concentration and effect have also been reported for dental evoked potentials [28] and for heat stimuli [29].

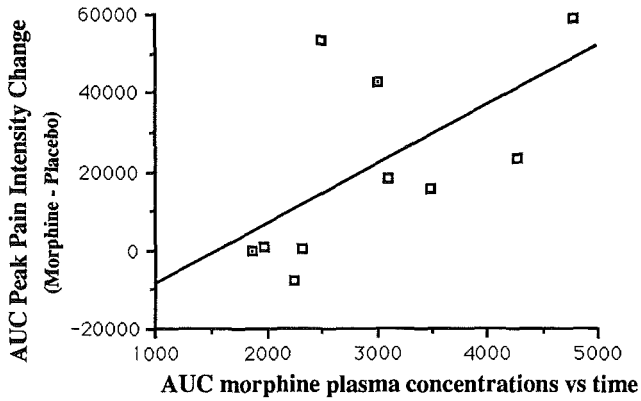

Figure 5 Relationship betwen plasma morphine concentration and effect on cold pressor pain. Redrawn from Jones et al [22].

CONCLUSION

Dose response to opiates can be shown in both clinical and experimental pain, and to other classes of analgesic in clinical but not experimental pain. Just as the issue of context dependent analgesia is a real clinical problem largely ignored by investigators, the circumstances under which the dose response curves can be demonstrated are often far removed from normal clinical practice. Studies use low doses to maximise sensitivity, and the proportion of 'total possible'

pain relief may be as low as 30%, which cannot be a clinical ideal. Part of the isolation from the important clinical issues is due to study focus on efficacy of new drugs, for which the classic observer methodology can be used successfully. The more important clinical questions may need new measurement techniques for efficacy studies of drugs or formulations with long duration of effect, or to determine efficacy in those pain conditions which respond poorly to the conventional analgesics.

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Discussion - Dose response effects in analgesiometry : Clinical vs experimental pain

J. Lahuerta

You mentioned the problem created by deafferentation pain. Even in the cases in which drugs such as tricyclics or anticonvulsants are effective, it takes a long time before the response can be assessed. Could some kind of acute pharmacological test be devised to discriminate responders from non-responders?

H.J. McQuay

At the moment, the default screen for deafferentation pain is to challenge the patient with an opiate and evaluate the response to different doses. That does not help terribly when we want to find an effective medication. All it tells us is don't use this one. Since this is such an heterogenous group, I suspect it will be difficult to have a test that may show whether anticonvulsants or antidepressants will work or not.

J. Lahuerta

The cold pressor test, besides being terribly painful, produces a marked elevation of the blood pressure. Does morphine block this response too?

H.J. McQuay

No. It blocks the pain but not the rise in blood pressure.

L.F. Prescott

It seems to me that in measuring analgesic effects it is important to define the dose-response to placebo. Because in the end, all your analgesia measurements have to be set against the placebo response. It has always intrigued me to see how in almost every study, the placebo response is exactly the response you would expect for an analgesic with a peak at one hour and an effect lasting for four hours at least after oral administration. It seems that perhaps sometimes not enough care is taken to define this accurately.

H.J. McQuay

In part, this is due to the expectations of the patients and the observers. In trials in which the active drugs have impressed the nurse observer the placebo scores are high. We can minimize or maximize the placebo effect by influencing the patients' and observers' expectations.

L. Lasagna

Mean results often mislead us with regard to what is going on and this is specially a problem with analgesic studies, because these curves one sees for average performance of placebo or active drug are extraordinarilly misleading. They make it look as if things were neat and tidy. They are not at all. Some patients treated with placebo get absolutely no pain relief over a five hour period, others zoom up quickly and stay up for quite a while and then there's everything in between. I have often thought that it would be much more useful to give information such as what percent of patients with a given dose will achieve a significant amount of pain relief within an hour or whatever, and will have that last for another two hours.

T.R. Weihrauch

Are dose-response curves different in the case of on demand analgesia when compared to conventional methods of administration?

H.J. McQuay

The mean total consumption of analgesics seems to be lower in on demand settings.

D.G. Grahame-Smith

I would like to refer once more to the use of tricyclic antidepressants in analgesia. Do these drugs, or carbamazepine, alter the dose-response curve of opiates, shifting it to the left, for instance?

H.J. McQuay

It is obvious now that tricyclic antidepressants act as analgesics at doses lower than those used in depression. This effect is

much faster in onset that any antidepressant effect and is independent from any mood effects. Although it is hard to do, shifting of the dose-response curves of conventional analgesics in different types of pain can be elicited.

E.A. Carr

It has been said that women respond to morphine in a different manner than men. Could this possibly be related to oestrogen levels?

H.J. McQuay

I do not know of any explanation but it is true that a better response to analgesic drugs is obtained in women.

F. García-Alonso

Just a comment about the difficulties in seeing dose-response relationships with non-steroidal antiinflammatory agents. A recent trial of different doses of dipyrone in the treatment of renal colic in Spain could not detect any difference in response, the two doses tested were equally effective.

R.L. Galeazzi

Can you comment on the possible differences in respiratory depression by opiates in patients with pain, compared to pain-free subjects?

H.J. McQuay

There is very little good data on this, but the idea is that the medullary respiratory centre is nociception-sensitive, and the net depressant effect of an opiate will depend on the balance between the pain input and the direct effect of the drug. In this context, if you take away the pain, for instance with a local anaesthetic, you alter the balance and you set the stage for respiratory depression. That is why it is so dangerous to give opiates as an infusion which takes no account of the pain.