

# Transdermal Opioid Asymmetry

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## Abstract

The conjunction of genetic variability in both opioid action and the system for the recognition and transmission of painful stimuli together with the natural asymmetry of the human body can explain some observed differences in response to transdermal opioids which has clinical implications and further emphasises the importance of individualised treatment

## BACKGROUND

### MECHANISMS

Pain systems rely upon inputs received from the peripheral terminations of nociceptors feeding into the dorsal horn there involving second order neurones and the input is modulated to determine what is transmitted centrally. The process of nociception is also modulated at the peripheral nerve terminals themselves.

Opioid receptors are located throughout the central and peripheral nervous system allowing binding of opioids to their receptors in dorsal root ganglia, central terminals of primary afferent neurones and peripheral sensory nerve fibres together with their terminals. Once occupied by an agonist the neuronal opioid receptors attenuate the response of the nociceptive input terminal and propagation of the action potential.

Peripheral opioid receptors (POR) mediate the analgesic effects of exogenous opioids locally applied; mu( $\mu$ ), delta( $\delta$ ) and kappa( $\kappa$ ) are all represented. On peripheral nerves sensory nerve impulses are modulated in a similar way to those centrally located and mu opioid receptors are present in the epidermal and dermal layers of normal skin. Though demonstrable, the response is variable which may be due to the actual number of opioid receptors. Opioid receptors which are not normally abundant (as prior to an acute pain) are increased on peripheral nerve terminals by inflammation and in chronic pain (1,2).

Analgesia is subject to the influence of an important genetic element. Within the human mu( $\mu$ ) opioid receptor itself lies the pharmacogenetic variability of the clinical effects of

opioid analgesics modulating their effect through altered opioid binding and signalling thereby influencing the response to nociceptive stimuli. Some genes involved in this differing processing of nociceptive stimuli and response to opioids have been identified. Inter-individual variability through genetic mechanisms in pain perception and processing, the clinical effects of opioids and individual differences in opioid sensitivity can result (3,4).

## ASYMMETRY

We now recognise that humans, as other animals, exhibit an asymmetry with left and right halves being demonstrably different. Animal evolution led to the emergence of the bilateral body plan followed by the activation of specific genes on one side but not on the other. After the stabilization of these differences they are translated into asymmetric organ development. The human brain itself has many asymmetrical features (5).

## TRANSDERMAL OPIOID

Transdermal delivery of opioid is unique in that the patch is applied to one or other side of the body to gain access to the circulation with the product needing to pass through all the layers and the constituent components of intact skin. Transdermal opioids are of increasing popularity with a range of available products.

Transdermal formulations of fentanyl have analgesic efficacy which has not been demonstrated to be due to a peripheral opioid analgesic effect at the site of application (2). Transdermal formulations of buprenorphine are also efficacious but this is clinically perhaps less predictable than would be expected from the standard calculated dose

equivalence and, in addition, patients report difficulty with the application of the delivery system and reactions to the adhesive (6)

OBJECTIVE

After two patients volunteered the information that they derived no benefit from the transdermal opioid if the delivery system was applied to one side of the body rather than the other it was appropriate to determine whether this variability of response might be a more widespread problem.

METHOD

To ascertain the frequency of this occurrence in a general population with chronic non-malignant pain two additional questions were therefore asked of all patients attending our opioid medication review clinic run by specialist nurses.

First: Is the pain relief you get from using the patch in any way different when you put it on the left or right hand side of your body?

Secondly, after a positive response: If it is different and the relief on the better side is rated as100, what figure would you put on the worse?

RESULTS

Over 5 months of 34 consecutive patients 8 indicated that the pain relief was, indeed, inferior, ranging from 0 to 80 for the worse side and is shown in the table.

Figure 1

TABLE 1. Pain relief experienced on the worse side (better side = 100)

Patient	1	2	3	4	5	6	7	8
Pain relief	50	40	70	50	45	0	80	0

CONCLUSION

Primary afferents normally show little if any spontaneous activity but this differs in chronic pain states with ongoing traffic not just from pain source or generally through disinhibition but also a heightened nociceptive drive which may result in a tonic discharge. The functioning of POR varies, in some patients this is muted or requires opioid stimulus whereas in others their expression is equivalent to that pertaining after inflammation.

Variability in pain perception and processing with inter-individual variability of the clinical effects of opioids and

genetic mechanisms contribute to individual differences in opioid sensitivity. Issues of gene expression are individual and it would be surprising if the pharmacogenetic variability of this expression did not extend to involve asymmetry.

In addition, variability in drug absorption between skin regions can be affected by factors such as age, sex, disease state, local temperature and cutaneous blood flow, potentially influencing drug permeation, in which asymmetry may also play a part.

Every time a patient receives a drug their response is individual though through randomised controlled trials (RCT) we are encouraged to believe differently (7). Subpopulations of patients find treatments determined by RCT as lacking efficacy to be extremely effective in the management of their pain.

An excellent example of the individual response combining physical and pharmacodynamic elements, the action of transdermal opioids in certain patients may be a function of POR through either facilitation or indirect inhibition. The findings emphasise the importance of identifying the pain mechanism at play in the individual patient and other influencing factors.

Clarification of mechanisms that contribute to the variability of opioid effects can help to yield individualised treatment for optimum pain relief at a cost of minimal adverse effects the importance of which should not be underestimated.

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