Clinical pharmacokinetics of transdermal opioids: focus on transdermal fentanyl.
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Transdermal delivery allows continuous systemic application of opioids through the intact skin. This review analyses the pharmacokinetic properties of transdermal opioid administration in the context of clinical experience, with a focus on fentanyl. A transdermal therapeutic system (TTS) for fentanyl has been developed. The amount of fentanyl released is proportional to the surface area of the TTS, which is available in different sizes. After the first application of a TTS, a fentanyl depot concentrates in the upper skin layers and it takes several hours until clinical effects are observed. The time from application to minimal effective and maximum serum concentrations is 1.2 to 40 hours and 12 to 48 hours, respectively. Steady state is reached on the third day, and can be maintained as long as patches are renewed. Within each 72-hour period, serum concentrations decrease gradually over the second and third days. When a TTS is removed, fentanyl continues to be absorbed into the systemic circulation from the cutaneous depot. The terminal half-life for TTS fentanyl is approximately 13 to 25 hours. The interindividual variability of serum concentrations, partly caused by different clearance rates, is markedly larger than the intraindividual variability. The effectiveness of TTS fentanyl was first demonstrated in acute postoperative pain. However, the slow pharmacokinetics and large variability of TTS fentanyl, together with the relatively short duration of postoperative pain, precluded adequate dose finding and led to inadequate pain relief or, especially, a high incidence of respiratory depression; such use is now contraindicated. Conversely, in cancer pain, TTS fentanyl offers an interesting alternative to oral morphine, and its effectiveness and tolerability in this indication has been demonstrated by a number of trials. Its usefulness in chronic pain of nonmalignant origin remains to be confirmed in controlled trials. In general, TTS fentanyl produces the same adverse effects as other opioids, mainly sedation, nausea, vomiting and constipation. In comparison with oral morphine, TTS fentanyl causes fewer gastrointestinal adverse events. The risk of hypoventilation is comparatively low in cancer patients. Sufentanil and buprenorphine may also be suitable for transdermal delivery, but clinical results are not yet available. Transdermal morphine is only useful if applied to de-epithelialised skin. However, iontophoresis may allow transdermal administration of opioids, including morphine, with a rapid achievement of steady state concentrations and the ability to adjust delivery rates. This would be beneficial for acute and/or breakthrough pain, and initial clinical trials are in progress.