Transdermal Buprenorphine in Clinical Practice

Interview with Rheinhard Sittl, MD, University of Erlangen, Pain Clinic, Erlangen, Germany

1. What are the benefits of transdermal delivery?
Transdermal delivery offers a number of clinical benefits for both the physician and the patient. It is non-invasive and provides psychological benefits over oral formulations and injections. Easy handling increases patient compliance, as does the convenient dosage regimen e.g. in the case of Transtec® every 4 days. It is cost-effective as the procedure is simple, making admission to hospital unnecessary and simplifying care for caregivers, patients and families.

The matrix patch provides rate-controlled delivery to ensure stable plasma levels by constant substance release from the patches. In practice, this means fewer adverse events than with oral formulations - no troughs or peaks as with oral application.

2. Why is buprenorphine suitable for transdermal application?
Buprenorphine combines small molecular size (467.6 Da) with high lipid solubility, therefore easily penetrating the skin barrier (octanol/water coefficient T log P=3.9).

Buprenorphine is 30 times more potent than morphine, providing excellent, long-lasting analgesia at the low substance levels which pass the skin barrier.

3. Is the patch technology itself important?
The patch technology with Transtec is a matrix patch where the active substance is an integral part of the polymer structure of the patch. It cannot be extracted - unless e.g. the patch is eaten. This matrix patch structure also prevents dose-dumping, a phenomenon often seen with older reservoir patches which is characterised by sudden release of excessive doses from the patch. Matrix patches thus make accidental overdose virtually impossible. As the matrix patch is also very robust, we use to cut it to smaller sizes to allow titration with lower doses of buprenorphine than those provided by the (commercially available) patches.

4. What evidence is there to show transdermal patches work?
We have evidence from over ten years’ use of fentanyl patches and for the buprenorphine patch since 2001. Patches are now the treatment of choice for a wide range of chronic pain conditions. Clinical studies on the buprenorphine patch include use in both cancer and non-cancer pain. In addition, the post-marketing surveillance study showed the success of Transtec in over 13,000 patients.

Contact: Anke Krueger-Hellwig
Phone: +49 241 569-2858, Fax: +49 241 569-52858, anke.krueger-hellwig@grunenthal.com
Grunenthal GmbH, 52099 Aachen, Germany, www.grunenthal.com
5. How has transdermal buprenorphine performed since launch?
Post-marketing surveillance studies have shown that transdermal buprenorphine is effective in the management of both cancer pain and non-cancer pain. Recent studies have further shown that it is as effective as fentanyl patches - but with a better safety profile, e.g. less constipation, or analgesic tolerance, meaning that stable doses can be applied over quite long periods. Furthermore, there is increasing evidence that it is safer in elderly patients and patients with renal impairment, as it has no immunosuppressive effects and excretion is mainly independent from the kidneys.

6. Is it easy to use in opioids naïve patients?
There are some precautions to be taken when switching (opioid-naïve) patients from non-opioid analgesics to buprenorphine (Transtec®). Basically, the titration procedure for buprenorphine is the same as with any other opioid: start low, go slow, e.g. begin with the smallest available patch size or even smaller by cutting and titrate patients up with sublingual buprenorphine tablets to individual pain relief needs. At the beginning of therapy it is important to keep the former pain medication for some days in addition to Transtec® as at the start of therapy, it takes some time before effective plasma levels are reached. Another precaution to be taken is the prophylactic prescription of antiemetic agents during the first few days of therapy as buprenorphine is a strong opioid and as such can initially provoke nausea and vomiting.

7. How can the patch be used in dosage titration?
As stated above, dosage titration is important at the beginning of therapy with Transtec, but also in the management of pain due to progression of the disease. The use of the patch makes this procedure simpler for both physicians and patients. The buprenorphine patch is available in three different dosage forms, with a release rate of 35, 52.5 and 70µg per hour. Simply moving up from one dosage strength to the next is one treatment option. As the buprenorphine patch is a matrix patch, where buprenorphine is incorporated in the adhesive matrix, the patch can be cut to provide a lower dose. For example the 35µg/h patch can be cut in two to provide 17.5µg/h.

8. Can the patch be used to replace other opioids?
Yes, by using conversion schemes and appropriate titration procedures (see 6).

Contact: Anke Krueger-Hellwig
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Grunenthal GmbH, 52099 Aachen, Germany, www.grunenthal.com
9. How is breakthrough pain managed?
When prescribing long-acting opioid analgesics, it is advisable to provide patients with a fast-acting formulation to treat breakthrough pain - particularly during the titration period. Preferably – in accordance with WHO recommendations - the same substance should be used, for example sublingual buprenorphine tablets (0.2mg or 0.4mg tablets). One sixth or one tenth of the total daily analgesic dose should be given. If not available due to country specific reasons, any other immediate release opioid formulation, e.g. tramadol, morphine etc. can be used.

10. Are there safety benefits with the transdermal patch?
The safety benefits of the transdermal patch include those for buprenorphine in other indications - the ceiling effect for respiratory depression, no effect on immune response, use in renal impairment and the elderly without dosage adjustment. Constipation and somnolence are low compared with other commonly used opioids. Specifically, the buprenorphine patch delivers constant plasma levels, which avoids the troughs and peaks of oral formulations and reduces adverse events. There is also the benefit of minimal risk of dependence or tolerance.

11. Are there local skin reactions to the patch?
Yes, mostly in the form of erythema and rashes. In about one third of patients these are usually transient and mild and comparable in incidence with other transdermal opioid formulations. The skin reactions can be treated by changing the patch application site and/or using appropriate skin care products.

12. Are there any restrictions for patients wearing the patch?
Any restrictions applying in general to the use of strong opioids also apply to the buprenorphine patch. It should for instance only be given when all other non-opioid and weak opioid treatment options have failed, according to the WHO ladder. At present it is not licensed for use in children, as there are no studies on Transtec® in children - only personal experience. Titration of the patch through cutting, however, is a major advantage compared with the reservoir patches when treating children. Taking high-dosed buprenorphine together with benzodiazepines has been reported to be fatal. In hepatic impairment close monitoring is necessary. A study on patients using saunas, spa baths and jacuzzis suggested that buprenorphine should not be given under these conditions because of excessive heat, which might increase peripheral blood flow - and hence plasma buprenorphine levels. However, if the patch is applied correctly, patients can carry out most activities, including bathing and showering without problems.

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Grunenthal GmbH, 52099 Aachen, Germany, www.grunenthal.com
13. Is the buprenorphine patch the new gold standard?
Transtec is an excellent analgesic, but we have to consider that in many pain conditions there is no alternative to morphine. However, we also have to understand that even morphine is not free of side effects, and while it is an excellent agent to provide pain relief in more acute pain situations, it is often less suitable in chronic pain management in the long-term. Development of analgesic tolerance and thus the need for increasing doses with all the negative consequences such as sedation or any other unpleasant side effects are the reasons for concern. Buprenorphine especially in its new transdermal formulation is in many cases indeed an alternative, especially as it is a potent and efficient analgesic and has some inbuilt safety advantages which make it particularly suitable for long-term pain management e.g. in cancer patients or the elderly.

14. What is your interest in buprenorphine?
As a main investigator and clinical expert I have been involved in the use of transdermal buprenorphine since the first clinical study. With many years of experience as a pain specialist I am interested in all innovations in this field. Personally, I think that buprenorphine and especially Transtec has a high potential to improve pain management in a vast variety of pain patients.

15. Where next for buprenorphine?
New studies indicate a strong antihyperalgesic effect of buprenorphine in comparison to other opioids. This could make buprenorphine suitable for pain syndromes caused by central sensitisation (neuropathic pain). Further studies are warranted. Buprenorphine will continue to be used on a wider scale as more clinicians gain more understanding and experience in its use. The buprenorphine patch is particularly appropriate for higher risk patient groups and offers especially safety advantages over the fentanyl patch or even morphine.