SKIN ADVERSE EVENTS INDUCED BY TRANSDERMAL THERAPEUTIC SYSTEMS OR TRANSDERMAL DELIVERY DRUG SYSTEMS

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BACKGROUND

Advantages associated with transdermal therapeutic systems (TTS) include avoidance of first-pass drug metabolism and variable absorption, as well as improved patient compliance[1]. Drugs available by this route include scopolamine, nitroglycerin, estradiol, nicotine, clonidine, fentanyl and testosterone. These drugs delivery systems must maintain affinity for both lipid and aqueous environment in order to obtain an effective systemic absorption. TTS are adhesive-containing systems with defined surface area that deliver drug to the surface of skin at a controlled rate. TTS are associated with some cutaneous adverse effects. (**Table I**)

AIM OR OBJECTIVE

To report some cutaneous adverse events induced by some drugs administered with TTS or transdermal delivery systems (TDDS) and discuss its mechanism.

MATERIAL AND METHODS

Patients studied at the contact dermatitis outpatient clinic from the Hospital del Mar IMAS, Universitat Autònoma de Barcelona, Spain during the 2004 and 2005 years. A prospective evaluation of the skin adverse events induced by TDDS was performed. Patients were submitted to a standardized protocol using cutaneous provocation tests as patch test and/or prick test. Patch test was performed according with the "European Society for Contact Dermatitis" and the "Environmental Contact Dermatitis Resreach Group" recommendations. The active principle and also the excipients from the involved drug were evaluated if it was possible.

RESULTS

From the 768 patients registered at the contact dermatitis clinic during these two years, four patients showed a cutaneous adverse event induced by patch delivered drugs. Buprenorphine (n=2), fentanyl (n=1) and nicotine (n=1) were the drugs involved in such reactions. (**Table II**) (**Figs. 1 - 5**)

Table II. Case reports

	Case 1	Case 2	Case 3	Case 4
Clinical report	**Local eccema** Infiltrate erythema Permanent	**Urticaria (acute)** Bronchospasm	**Irritative** Erythema Transient	**Local dermatitis** Infiltrate erythema Permanent (**Fig.4**)
Product	Transtec®	Transtec®	Duragesic®	Nicotinell® 30
Drug	**Buprenorphine**	**Buprenorphine**	**Fentanyl**	**Nicotine**
TTL-TDS* **Patch test**	**Drug patch ++** Adhesive Neg (**Fig.1**)	**Drug patch ++** Adhesive Neg (**Fig.2**)	**Drug patch** Adhesive Neg	**Drug patch ++ (96h)** Adhesive + (48h) (**Fig.5**)
Drug **Patch test**	ND, patient Exitus	**Buprenorphine 0,3% ++** **(Buprex®)** (**Fig.3**) Placebo patch*** Neg	ND	Nicotine 10% acu ++
Other Patch test studies	GEIDAC stand Neg Resin Trolab Neg Morphine MST Neg	Balsam Peru ++ Neomicin ++ AINEs Marti Tor/Chem. Neg Tiazides Chem. Neg Losartan Neg Resin Trolab Neg	ND	Balsam Peru + Resin Trolab Neg Dental Trolab Neg
Controls**	25 negative	25 negative	25 negative	20 negative

N.D. Not done
GEIDAC: Grupo Español para la Investigación de la Dermatitis de Contacto y Alergia Cutánea
*Patch test performance and readings according ESCD and ECDRG recommendations. Reading 96 hours
**Controls followed the same protocol
***Placebo patch test and Buprex® (Buprenorphine) kindly provided by Grünenthal

Table I. TTS reactions

- **Urticaria and angioedema (very rare)**
- **Systemic sensitization (very rare)**
- **Irritant Dermatitis (common)**
  - Most common adverse reaction reported.
  - Increase with occlusion duration.
- **Erythema (common)**
  - Due to vasodilators and reactive hyperhemia.
  - Transient reactions.
- **Burns (very rare)**
  - Commonly associated with microwave oven or defibrillation.
- **Allergic Contact Sensitivity (rare)**
  - Excellent model to produce sensitization.
  - Potential allergens include adhesive, membrane, solvent, enhacer and active drug.
  - Majority of reactions reported have been to the drug itself.

Fig.1. Transtec® positive patch test, drug patch with buprenorphine.

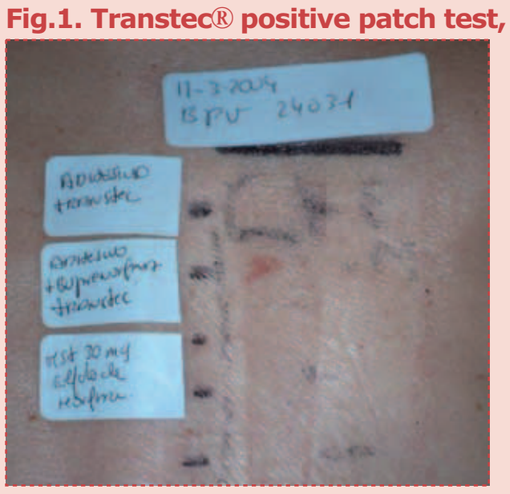


Fig.2. Transtec® positive patch test, drug patch with buprenorphine.

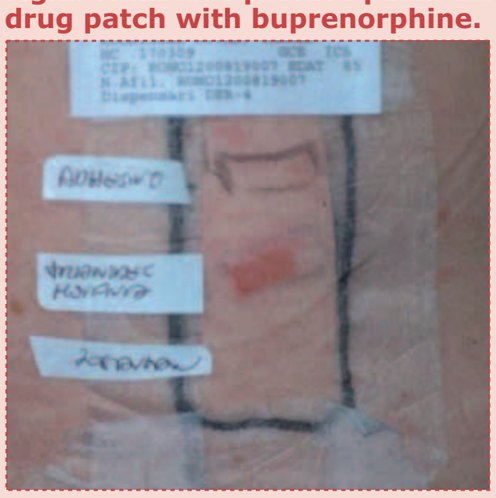


Fig.3. Positive buprenorphine 0,3% patch test and negative placebo Transtec® patch test provided by Grünenthal SA.

Fig.4. Delayed permanent infiltrated erythema induced by Nicotinell®, nicotine TDDS.

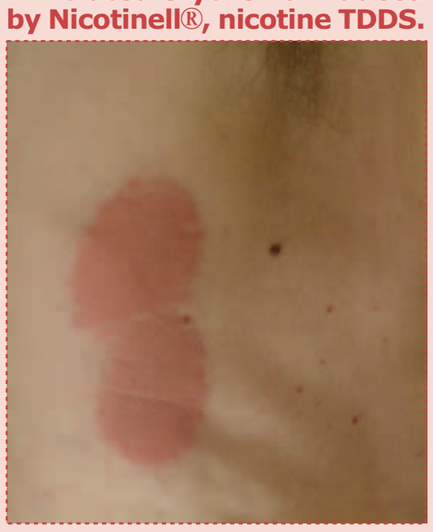
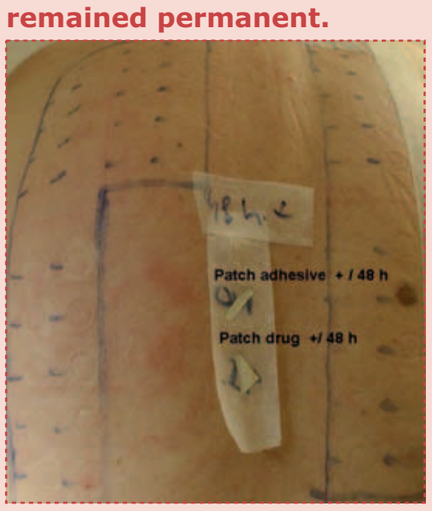


Fig.5. Positive nicotine and adhesive Nicotinell® patch test. Positive adhesive reaction was transient and disappeared at 96 hours while nicotine reaction remained permanent.



DISCUSSION

The patients studied habitually used multiple systemic drugs. Local eccema or dermatitis helped us to suspect the TTL administered drug as responsible of the AEs. TDDS buprenorphine imputability on the development of diffuse urticaria required a careful study. Temporal relationship with each drug habitually employed was evaluated and also oral reintroduction drug by drug was performed.
Transdermal buprenorphine is generally well tolerated. The most common cutaneous AEs are local transient erythema and pruritus (> 5%)[4]. Local tolerability of transdermal opioid systems should be considered when making a therapeutic choice. Transdermal fentanyl seems to be best tolerating than buprenorphine[5]. Buprenorphine TDDS (Transtec®) and buprenorphine (0,005% and 1% aq.) allergic contact dermatitis has been recently demonstrated (n=6)[6]. Nevertheless this kind of hypersensitivity reaction was questioned by some authors that support the irritant nature of such reactions[7].
Our first case can be considered a contact dermatitis probably allergic because of the delayed course, the clinical characteristics and the permanent nature of the patch test reaction. The cutaneous infiltrated erythema severity increased with the use of patches.
Opiate urticaria and/or anaphylaxia is very rare but has been shown[8]. As far as we know any case of buprenorphine (systemic or TDDS) induced urticaria has been described.
Intense local skin reactions with erythema, oedema and infiltration were repeatedly seen after application of nicotine patch[9]. The incidence of serious adverse skin reaction was 7% in participants receiving nicotine TTS in a recent smoking cessation study[10]. Most of the skin reactions can probably be categorized as irritant contact dermatitis. However, evidence for allergic contact dermatitis was found in 3,3% of subjects treated with nicotine TTS in field study[11]. The recommended patch test concentration for nicotine is 10% aq. **The local cutaneous permanent delayed infiltrated erythema induced by TTD nicotine in the patient studied could be categorized as allergic contact dermatitis.**

CONCLUSION

There is any definitive clinical, pathological or molecular marker to distinguish irritative response from delayed hypersensitivity.
Drug pharmacologic properties would be considered in order to interpret the TTD drug cutaneous adverse event and to understand the cutaneous provocation tests results.
It is not uncommon to tolerate drug intake rather topical administration in such cases.

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