Oral topical doxepin rinse: Anesthetic effect in normal subjects

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Oral doxepin rinse has been reported to provide pain relief in patients with oral mucosal lesions due to cancer or cancer therapy. The purpose of this study was to assess the anesthetic effect of doxepin oral rinse in normal subjects to identify the duration of effect and to contrast the anesthetic effect with reported pain relief in patients with oral mucosal lesions.

Normal volunteers were provided a solution of doxepin (5 mg/mL) for oral rinsing. Oral numbness and adverse effects were recorded for a period of 4 h after rinsing.

Doxepin rinse resulted in mucosal anesthesia in all subjects. Sedation/fatigue was reported in four of seven subjects. There were no taste complaints and no nausea reported.

The limited duration of numbness/anesthesia in normal subjects compared with prior studies showing pain relief for more than 3 h in patients with mucosal lesions, suggests that the extended duration of pain relief in patients was due to analgesic effects rather than anesthetic effects. The majority of normal subjects reported sedation after use, but this was less common in patients with mucosal lesions.

Key Words: *Doxepin; Topical analgesia; Topical anesthetic*

Doxepin (C₁₉H₂₁N.HCl) is a tricyclic antidepressant (TCA) drug. Tricyclics appear to have both central and peripheral effects. The primary mechanism of action may be on descending pathways by blocking reuptake of serotonin and norepinephrine (1,2). Doxepin has potent H1 and H2 receptor blocking activity. In addition, nonspecific enkephalin-like activity has been demonstrated in patients who were prescribed doxepin (3). TCAs may also affect n-methyl-D-aspartate receptors in addition to effects on the descending norepinephrine and serotonergic systems (4). Once systemically absorbed, doxepin is converted in the liver to desmethyl-doxepin, an active metabolite, which is excreted in the urine following glucuronidation (2). Plasma levels of drug and metabolite are highly variable, and correlate with variable absorption following systemic administration.

Doxepin is used in the management of depression and chronic pain (1,3,5-8). Systemic use leads to sleep facilitation,

Un rinçage-bouche de doxépine topique : L'effet anesthésique chez les sujets en santé

Il a été déclaré que le rinçage-bouche de doxépine soulage la douleur des patients ayant des lésions muqueuses orales causées par le cancer ou le traitement du cancer. La présente étude vise à évaluer l'effet anesthésique du rinçage-bouche de doxépine chez des sujets en santé afin d'établir la durée de l'effet et de contraster l'effet anesthésique au soulagement déclaré de la douleur de patients ayant des lésions muqueuses orales.

Des volontaires en santé ont reçu une solution de doxépine (5 mg/mL) afin de se rincer la bouche. L'engourdissement oral et les effets secondaires ont été inscrits pendant une période de quatre heures après l'utilisation.

Le rinçage-bouche de doxépine a entraîné l'anesthésie muqueuse de tous les sujets. Quatre des sept patients ont déclaré un effet de sédation ou une lassitude. Personne ne s'est plaint du goût ou de nausées.

La durée limitée de l'engourdissement et de l'anesthésie des sujets en santé, par rapport aux études antérieures faisant état d'un soulagement de la douleur pendant plus de trois heures chez les patients présentant des lésions muqueuses, laisse supposer que la longue période de soulagement des patients était imputable aux effets analgésiques plutôt qu'aux effets anesthésiques. La majorité des sujets normaux ont rendu compte d'une sédation après l'usage, mais cette sensation était moins courante chez les patients ayant des lésions muqueuses.

and reduced pain (1). Tricyclics have analgesic effects in neuropathic pain, independent of their antidepressant effect (1,5,6). Doxepin has been used in combination with nonsteroidal anti-inflammatory drugs in the management of pain associated with advanced cancer (7). Systemic doxepin has also been used in pain management associated with oral mucositis (8). Systemic doxepin, when used for treatment of depression, produces drowsiness in a significant number of patients. Doxepin is contraindicated in patients with narrow angle glaucoma, and for patients with urinary retention. Serious drug interactions may occur when used with monoamine oxidase inhibitors. There is no evidence in animal studies of teratogenic effects (2), and no studies of use during pregnancy have been reported.

Topical application of doxepin has been prescribed for the management of skin pruritus (5,9) and for neuropathic pain of the skin (5,10). We have previously reported pain relief following

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oral rinsing with doxepin suspension in patients with oral lesions due to cancer or treatment of cancer (11). The purpose of the present study was to assess the anesthetic effect of doxepin in patients with intact mucosa, and to compare the duration of effect with the previously reported reduction in oral pain in cancer patients.

MATERIALS AND METHODS

The present study was a single dose, open label trial of an oral rinse of doxepin suspension. Normal subjects volunteered for a single oral rinse application. Doxepin suspension was prepared at 5 mg/mL in an oral rinse containing 0.1% alcohol and sorbitol. Subjects rinsed 5 mL for 1 min and spit out. Subjects completed Visual Analogue Scales (VAS) to assess pain and side effects following the use of the rinse at 5 min, 15 min, 30 min, 1 h and continuing every 0.5 h up to 4 h. Subjects evaluated their appraisal of taste, stinging (or burning) with use of the rinse, numbness (anesthesia), and drowsiness or fatigue following rinsing. The VAS taste measure used anchors of 0=terrible, 5=acceptable and 10=excellent. Fatigue following use was reported on a VAS scale with 0=none and 10=severe, leading to sleep.

Statistical analyses were performed using S-Plus 4.0 release 3 for Windows (MatSoft Inc, USA). The nonparametric Wilcoxon signed rank test, was used to assess the outcome measures.

RESULTS

Seven volunteers (four women and three men) participated. The mean age was 38.7 years (range 18 to 50 years). No oral mucosal lesions and no mouth pain were present. No anesthetics and no analgesic use was reported in the 72 h prior.

No discomfort or stinging was reported by any participant during or following rinsing. The taste was reported to be good to excellent (VAS mean 8/10; range 6 to 10). The VAS pain and drowsiness/fatigue results are shown in Table 1.

DISCUSSION

This trial assessed subjective anesthesia in patients with intact mucosa, without mucosal sensitivity. Analgesia could not be assessed because no pain was present. In subjects with intact mucosa, self report of anesthesia began by 5 min, and reached a maximum in 15 min to 30 min, with a rapid return to normal after 1 h and resolution by 1.5 h to 2 h. The reported duration of anesthesia in this trial is similar to, but longer than that reported in prior studies of topical anesthetic agents, which usually is less

than 0.5 h (12,13). While topical anesthetics typically cause burning sensitivity when applied to damaged mucosa, this was not reported in the prior study with cancer patients (11). Topical anesthetics may also reduce or eliminate the gag reflex, and taste and sensation with eating and swallowing. Systemic absorption of topical anesthetics may cause cardiac effects (14-16). Burning sensitivity or stinging has not been reported in our prior study of topical doxepin rinse in cancer patients with oral mucosal lesions (11).

Fatigue/drowsiness was a common complaint, developing in more than one-half of the subjects, with moderate to high ratings in those who reported fatigue. Maximum fatigue ratings were severe, but an average rating of moderate fatigue was reported. Fatigue was reported later than the anesthetic effect, suggesting a local action resulting in anesthesia and a central action resulting in fatigue. Topical doxepin applied to the skin in areas of neuropathic pain has been shown to have good analgesic effect (9,10,17). Drowsiness has been reported following skin application (5).

In our earlier report, the intensity and duration of pain reduction was assessed in cancer patients with symptomatic oral mucosal lesions (11). The previous study showed that the analgesic effect resulted in a reduction of pain intensity of more than 50%, with greatest relief after 1 h to 2 h with a duration of more than 3 h, and pain not returning to baseline at 4 h after rinsing. The rinse was reported to have an acceptable taste and infrequent stinging with use. In the present normal volunteer study, there was no pain at baseline, but a sensation of numbness following rinsing resolved rapidly, suggesting that pain relief reported in the previous study of cancer patients was likely due to an early anesthetic effect, and a return to normal sensation with persisting pain relief was due to an analgesic effect with a duration of approximately 4 h. In the normal volunteer study, fatigue developed later than the anesthetic effect and was a more common complaint than in the cancer patients. Pain reduction in cancer patients appears to be related to both local anesthetic and analgesic effects, and fatigue likely represents a central effect. The effect upon pain in mucositis may also be related to prolonged local anesthesia leading to reduction in neurologic 'windup' that may occur in prolonged pain.

These findings suggest a relatively short period of anesthesia and an extended period of analgesia following use of doxepin oral rinse. In addition, the greater report of fatigue in normal volunteers suggests that further dose ranging studies are indicated. It is

TABLE 1
Subject reports of symptoms following doxepin oral rinse

Time post rinse	Oral numbness VAS	Mean	P*	Drowsiness/fatigue VAS	Mean	P
5 min	3,7,4,3,2,1,0	2.8	—	0,0,0,0,0,0,0	0.0	—
15 min	5,9,7,8,7,6,6	6.9	0.02	0,5,2,0,0,0,0	1.0	0.19
30 min	5,8,5,5,6,8,8	6.4	0.02	3,7,2,2,0,2,0	2.6	0.04
1 h	4,6,3,2,4,7,6	4.6	0.30	7,7,4,7,0,3,0	4.0	0.04
1.5 h	0,2,0,0,1,6,4	1.9	0.67	3,7,5,3,2,2,0	3.1	.03
2 h	0,1,0,0,1,4,2	1.1	0.20	1,7,8,2,2,0,0	2.9	0.04
3 h	0,0,0,0,0,1,0	0.0	0.04	0,7,6,2,2,0,0	2.2	0.07
4 h	0,0,0,0,0,0,0	0.0	0.03	0,5,2,1,0,0,0	1.1	0.11

*compared with the score at 5 min; VAS Visual analog scale

possible that in patients with severe mucosal pain, higher concentrations of drug may be beneficial, and may not be associated with fatigue to the degree seen in normal volunteers. It is possible that the duration of rinsing in the subjects without mucosal lesions was longer and was associated with increased tiredness and fatigue more than in the cancer patients.

Both of the trials of doxepin rinse (11) examined a single dose of topical doxepin, and experience with systemic dosing of TCAs suggests a reduction in sedation with continued use over time. Consistent with sedation reported with systemic use, several of the cancer patients who reported sedation with topical rinsing in this study continued use due to the significant analgesic effect and reported reduction in fatigue with continuing use. We concluded that the results of the trial in cancer patients showed that topical doxepin rinse provided clinically significant pain relief in patients with mucosal damage

and had an excellent profile of duration of effect, allowing a convenient dosing schedule.

Topical medications may reduce mucosal pain, providing pain relief while allowing a reduction in the use of systemic analgesics, including opioids. The results of our two open-label trials suggest that the doxepin rinse may be a useful medication when applied topically to damaged oral mucosa, and that the pain effect is due to an early anesthetic effect, followed by an analgesic effect. The rapid onset and duration of pain relief, and lack of burning with use, even in patients with damaged mucosa, are desirable qualities. If drowsiness occurs, use of the agent may be indicated at night, and in settings where the patient is not operating machinery or driving. Further dose ranging studies will allow for a better determination of the frequency of drowsiness and the concentration needed for the optimum analgesic effect.

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