our patients were examined at the manufacturer's laboratory and were found to be in perfect condition. Placebo patches containing all the components of the patches apart from hyoscine were applied in all of the men; no local skin reactions were observed.

Comment

This study showed an unexpectedly high rate (10%) of allergic contact dermatitis to transdermal hyoscine in healthy men treated for several months. Allergic contact dermatitis (type IV delayed hypersensitivity) was diagnosed by well established clinical criteria and was further confirmed by the absence of any reaction to a placebo patch.

Our results contrast with those of studies conducted by the manufacturer (Alza Corporation, California, United States), in which no delayed contact sensitisation occurred. In those studies 203 subjects were examined according to a protocol that included the consecutive application of nine hyoscine patches and the application of a tenth patch after two weeks' rest. The design of these studies, however, does not rule out the possibility of delayed type IV hypersensitivity occurring as a result of more prolonged use of transdermal hyoscine. Studies of the long term use of transdermal clonidine showed an incidence of allergic contact dermatitis of 10-38% after three to 12 months of continuous treatment.[3] On the other hand, delayed hypersensitivity to transdermal glyceryltrinitrate, which is commonly used in long term and repeated regimens, is rare.[4]

We conclude that delayed hypersensitivity may be a serious disadvantage of giving drugs transdermally. Evaluation of new transdermal treatments should exclude the possibility of delayed hypersensitivity, which in our experience may develop even after several months of repeated application.

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Atrial natriuretic peptide in the fetus

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Atrial natriuretic peptide has diuretic, natriuretic, and vasodilator properties, counterregulating the renin-angiotensin-aldosterone system.[1] We investigated whether it is present in the fetal circulation by using cordocentesis to obtain fetal blood samples, in some cases before and after transfusions for rhesus isoimmunisation.

Methods and results

Blood samples (0·5 ml) were collected on 15 occasions from nine fetuses (from the umbilical vein in 14 and the heart in one) undergoing treatment for rhesus isoimmunisation. The mean gestational age was 28 weeks (range 20-32) and the mean packed cell volume 0·29 (range 0·22-0·39). Samples were obtained before and after transfusion from eight fetuses and after transfusion alone in one case. A sample of donor blood was collected at each transfusion.

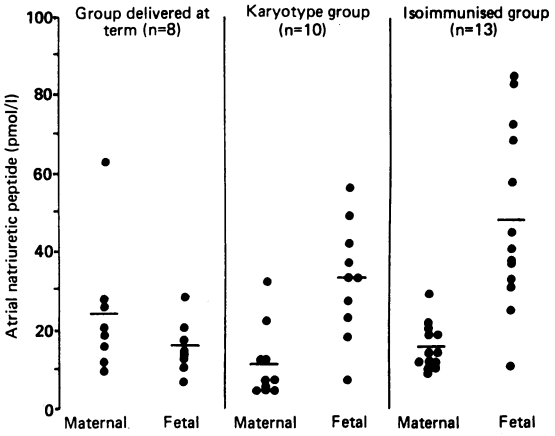
Blood samples were also obtained from 12 fetuses (from the umbilical vein in 10 and the heart in two) undergoing cordocentesis to determine the karyotype. In seven cases this was because of a structural anomaly (gastroschisis (one), urinary tract obstruction (three), duodenal atresia (one), and diaphragmatic hernia (two)). In 10 cases the karyotype was normal, but one fetus had triploidy and another trisomy 21. The mean gestational age of this group was 23 weeks (range 17-34).

In each case samples of maternal blood were collected before the procedure. Umbilical cord and maternal venous blood samples were also obtained in eight normal term deliveries.

Atrial natriuretic peptide was measured by pre-extracted radioimmuoassay,[2] the results being expressed in pmol/l (10 pg/ml=3·2 pmol/l). The figure shows the results for the paired maternal and fetal umbilical samples in each group, the one unpaired and three intracardiac samples being excluded. Statistical analysis was by Wilcoxon rank sum test or coefficient of correlation as indicated.

Before transfusion the fetal atrial natriuretic peptide concentrations in the isoimmunised group were significantly higher (mean 49 (range 12-86) pmol/l) than in those in the karyotype group (34 (8-57) pmol/l; $p<0·05$) and in the group delivered at term (16 (7-29) pmol/l; $<0·01$). Fetal concentrations in the karyotype group were also significantly higher than those in the group delivered at term ($p<0·05$). Taken together, the fetal concentrations in the isoimmunised and karyotype groups showed no significant correlations with fetal packed cell volume, fetal albumin concentration, gestational age, or maternal atrial natriuretic peptide concentration. In both the isoimmunised group and the karyotype group fetal concentrations of atrial natriuretic peptide were significantly higher than corresponding maternal values ($p<0·01$). The concentrations in the three intracardiac samples were 73, 100, and 124 pmol/l.

After intravascular transfusion the atrial natriuretic peptide concentration rose in seven cases. The concentrations before and after transfusion were 42 and 50 pmol/l; 12 and 77 pmol/l; 34 and 42 pmol/l; 84 and 98 pmol/l; 59 and 48 pmol/l; 70 and 149 pmol/l; 86 and 167 pmol/l; 73 and 114 pmol/l (intracardiac measurement); and not measured and 120 pmol/l. The mean



Maternal and fetal (umbilical vein) concentrations of atrial natriuretic peptide. Bars indicate mean values

volume of blood transfused was 56 (range 20-105) ml. Donor blood showed very small concentrations (0-2 pmol/l).

Comment

These preliminary results show that atrial natriuretic peptide circulates in the fetus and placenta. The higher fetal than maternal concentrations and the values in the three intracardiac samples are consistent with production by the fetus.

The higher fetal concentrations in the isoimmunised group may reflect expansion of the fetoplacental plasma volume, which suggests that release of the peptide in fetuses is regulated in the same way as that in adults. The dynamic response to intravascular transfusion in this series (despite the dilutional effect of the donor blood) is supported by experimental work[3] and indicates that intravascular volume expansion is an important stimulus for release of the peptide.

Atrial natriuretic peptide may influence umbilical blood flow as specific receptors have been identified in the placenta.[4] An additional role might be to regulate the volume of amniotic fluid, as in sheep fetal production of urine increases in response to atrial natriuretic peptide.[5]

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Morphine and dryness of the mouth

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Morphine sulphate taken by mouth is the drug of choice when a strong opioid analgesic is required to control pain caused by cancer.[1] Specific gastrointestinal side effects such as nausea, vomiting, reduced gastrointestinal motility, and reduced biliary and pancreatic secretions are well documented.[2] Dryness of the mouth is not generally recognised as a side effect of morphine,[2,3] but clinical experience suggests that it is a common complaint of patients with cancer who are receiving it. We studied the prevalence of dryness of the mouth in patients with cancer to see whether it is associated with the use of morphine.

Patients, methods, and results

All patients admitted to this hospital during a period of eight weeks were entered into the study except those who had other reasons for having a dry mouth—namely, those receiving radiotherapy or surgery to the head and neck, those who had received a general anaesthetic within the previous 48 hours, those whose intake by mouth was restricted, and those receiving cytotoxic chemotherapy.

We recorded demographic data; details of the current analgesic being taken (drug, dose, preparation, and duration of treatment at the current dose) and of other drug treatment; whether dentures were worn; and whether there was evidence of oral candidiasis. Patients completed a questionnaire comprising two four point categorical scales (Do you suffer from a dry mouth? How dry has it been in the past 24 hours?) and a 10 cm visual analogue scale, which also measured the severity of the dryness during the preceding 24 hours and was included to support the results from the second categorical scale.

A high degree of concordance was found between the categorical and visual analogue scales (Goodman and Kruskal's gamma statistic=0·97). The results were based on the answers to the question for the second categorical scale.

Data were obtained from 199 patients, all but 10 of whom had malignant disease. Forty eight men aged 22-84 (median 63) and 151 women aged 22-88 (median 60) completed the questionnaire.

Opioid analgesics were being taken by 131 patients, of whom 67 were taking morphine. Of those taking morphine, 45 received it as an aqueous solution, 18 as controlled release tablets, and two as suppositories; two patients received parenteral diamorphine. Dryness of the mouth at some time during treatment was reported by 113 of the 199 patients, of whom 42 had a dry mouth most or all of the time. No significant association was observed between the severity of the dryness of the mouth and sex, age, primary diagnosis, reason for admission, wearing dentures, candidiasis of the mouth, or smoking.

Drugs other than analgesics were being taken by 156 of the 199 patients, and 72 of them took drugs that were known to cause a dry mouth—for example, those with anticholinergic activity and diuretics. As expected, a significant association was found between taking these drugs and the severity of the dryness of the mouth (test for trend $\chi^2=9{\cdot}31$, df=1, p=0·002). Further analysis was therefore undertaken with the type of analgesic drug stratified according to whether patients were also taking drugs known to cause dryness of the mouth.

Assessment of dryness of mouth during previous 24 hours in 199 patients according to type of analgesic drug and concurrent treatment given. Values are numbers (percentages) of patients

Analgesic group	Dryness of mouth (categorical scale)			
	Normal	Slightly dry	Moderately dry	Extremely dry
Concomitant treatment expected to cause dry mouth				
Morphine (n=35)	10 (29)	3 (9)	9 (26)	13 (37)
Non-opioid, weak opioid, or no analgesics (n=37)	18 (49)	6 (16)	7 (19)	6 (16)
No concomitant treatment or treatment not expected to cause dry mouth				
Morphine (n=32)	8 (25)	5 (16)	14 (44)	5 (16)
Non-opioid, weak opioid, or no analgesics (n=95)	61 (64)	11 (12)	21 (22)	2 (2)

The table shows the results. A highly significant association was found between the use of morphine and dryness of the mouth (test for trend (stratified) $\chi^2=20{\cdot}62$, df=1, p<0·0005). When concurrent treatment was allowed for patients receiving morphine were roughly four times more likely to have a dry mouth of any severity than patients taking weak opioid, non-opioid, or no analgesics (95% confidence interval for odds ratio 2·0 to 7·2 by logistic regression analysis[4]).

Comment

Our results show a clear association between the use of morphine and dryness of the mouth in this sample of patients. The mechanism for this effect is unclear. We