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TRANSDERMAL SCOPOLAMINE IN THE HYPERBARIC ENVIRONMENT
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H J SCHWARTZ ET AL. NOV 86 NEDU-2-86

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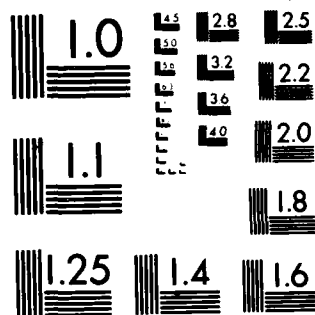
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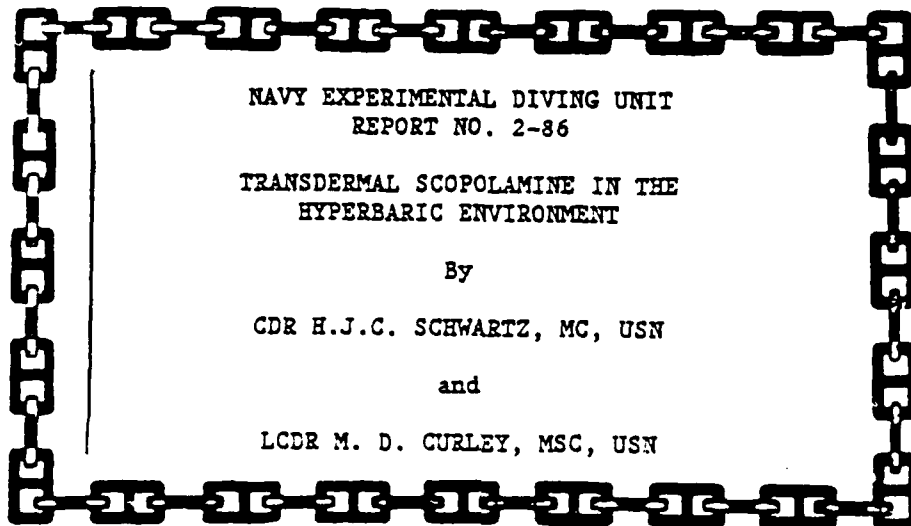


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DEPARTMENT OF THE NAVY
NAVY EXPERIMENTAL DIVING UNIT
PANAMA CITY, FLORIDA 32407-5001

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TRANSDERMAL SCOPOLAMINE IN THE
HYPERBARIC ENVIRONMENT

By

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NOVEMBER 1986

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The effect of transdermal scopolamine (Transderm Scop®) on the behavior of divers under pressure was evaluated during a 5 1/2 day, 60 feet of sea water (FSW) (2.8 ATA) air saturation dive at the Navy Experimental Diving Unit. Nine male and one female U.S. Navy divers were administered either the drug or a placebo in the single-blind study during and after the dive. In both drug and placebo conditions, diver cognitive performance was assessed 12 to 14 hours post-administration using a test of memory and attention from the Performance Measurement System. There were no significant differences in group performance on the cognitive test as a function of drug or pressure conditions. Standardized clinical questions were also asked upon completion of the testing to document any side effects of the drug or placebo. Pre-dive, six divers given transdermal scopolamine had no side effects, three had dry mouth, and two reported mild malaise or mental fuzziness. At 60 FSW, two divers had no side effects, and eight divers reported dry mouth. Other side effects reported were two cases of mild malaise or mental fuzziness, one case of clumsiness, and one case of difficulty with visual focus. Post-dive (nine divers participating), three divers had no side effects, five had dry mouth, four had drowsiness, two had itching of patch site, one had dilation of one eye, and one had trouble with visual focus. During placebo administration one diver reported mental fuzziness at 60 FSW, and post-dive one reported giddiness, and another had dry mouth. No unusual symptoms were seen as function of drug, pressure, or their interaction.

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ABSTRACT

→ The effect of transdermal scopolamine (~~Transderm-Scop~~[®]) on the behavior of divers under pressure was evaluated during a 5 1/2 day, 60 feet of sea water (FSW) (2.8 ATA) air saturation dive, at the Navy Experimental Diving Unit. Nine male and one female U.S. Navy divers were administered either the drug or a placebo in the single-blind study during and after the dive. In both drug and placebo conditions, diver cognitive performance was assessed 12 to 14 hours post-administration using a test of memory and attention from the Performance Measurement System. There were no significant differences in group performance on the cognitive test as a function of drug or pressure conditions. Standardized clinical questions were also asked upon completion of the testing to document any side effects of the drug or placebo. Pre-dive, six divers given transdermal scopolamine had no side effects, three had dry mouth, and two reported mild malaise or mental fuzziness. At 60 FSW, two divers had no side effects, and eight divers reported dry mouth. Other side effects reported were two cases of mild malaise or mental fuzziness, one case of clumsiness, and one case of difficulty with visual focus. Post-dive (nine divers participating), three divers had no side effects, five had dry mouth, four had drowsiness, two had itching of patch site, one had dilation of one eye, and one had trouble with visual focus. During placebo administration one diver reported mental fuzziness at 60 FSW, and post-dive one reported giddiness, and another had dry mouth. No unusual symptoms were seen as function of drug, pressure, or their interaction.

> KEY WORDS:

Test Plan #84-42

→ Saturation Diving

Side Effects

← Motion Sickness . ←

Drugs

Performance

Scopolamine

Transdermal

Portions of this report were presented in a poster session at the 1985 Joint Conference, Undersea Medical Society Annual Scientific Meeting and Tenth Annual Conference on Clinical Application of Hyperbaric Oxygen, Long Beach, CA, 11-14 June 1985, and abstracted in Undersea Biomedical Research, Supplement to Vol. 12(1), 1985, p. 36.

TRANSDERMAL SCOPOLAMINE IN THE HYPERBARIC ENVIRONMENT

Introduction

The U.S. Navy has many occasions when personnel must be exposed to rough weather at sea in order to meet operational commitments. Often, this rough weather has caused seasickness with the attendant discomfort and hazard to the individual, the ship, or the mission. Divers are particularly prone to seasickness for several reasons. They may be shore-based until just before they are needed for a job at sea, and may not have time to acclimate to the sea. They are likely to be on smaller ships or even in small craft which bounce around more in a given sea state than larger vessels. They are virtually unable to vomit into some breathing apparatus such as a SCUBA mouthpiece without inviting death from drowning or air embolism on emergency ascent. In other diving apparatus, such as the MK 12 SSDS helmet, vomiting is nearly as hazardous, although not instantly catastrophic. While it is true that at depth the wave effect is greatly diminished, the diver is still exposed to the action of waves on the surface before and after diving, upon entering and exiting the water column, and during long shallow in-water decompression stops.

Various remedies and preventatives have been used by the U.S. Navy for this common problem. Among them are the antihistamines dimenhydrinate and meclizine, and promethazine, a phenothiazine with antihistamine properties. While these drugs are fairly effective they are also sedatives and cause a high incidence of drowsiness. Recently, a topical preparation of scopolamine on an adhesive patch, transdermal scopolamine (Figure 1) has enjoyed widespread acceptance on shipboard due to its effectiveness, ease of application, long duration of 72 hours, and minimal side effects^(1,2). The effects of administration of transdermal scopolamine on various aspects of the performance of Israeli Naval personnel were reported by Gordon et al (3). No difference in performance was found between the drug and placebo conditions in a normobaric environment. There are anecdotal reports of transdermal scopolamine use by divers but there are no documented reports of its use in a hyperbaric setting.

It is known that inert gases such as nitrogen have an effect on the central nervous system (CNS) in the hyperbaric environment. This effect is whimsically called Martini's Law, since for every 50 feet of sea water (FSW) the behavioral effect of the nitrogen in air is approximately equal to drinking one martini on an empty stomach. The effect can be altered by various psychoactive drugs. It is very useful to determine what CNS effects, if any, will occur from the use of transdermal scopolamine at depth. Such effects could be different from the well documented effects of the drug at a pressure of one atmosphere (ATA) for the following reasons: (1) possible interaction with the CNS effects of nitrogen, (2) unknown effects of pressure on the rate of absorption from the transdermal patch with a potentially higher blood level than intended, or (3) unknown factors due to the hyperbaric environment.

As a preliminary test it would be of great use to determine the frequency and type of side effects which can be expected in the hyperbaric environment from transdermal scopolamine. The side effects which are listed in the manufacturer's package insert (Figure 2) at 1 ATA include the common ones of dry mouth (67%), drowsiness (17%), and occasional temporary blurring of vision and pupillary dilation. Rarer side effects are disorientation, memory disturbances, dizziness, restlessness, hallucinations, confusion, difficulty urinating, skin rashes or redness, and dry itchy eyes. It may be hypothesized that side effects are likely to be consistent for a given individual so that if an individual determines that he has side effects which prevent taking the medication, he will not later accommodate to the medication and should not risk further side effects by taking it again. The side effects are also of a type that are very subjective and could also be induced by taking placebos. For these reasons, it is desirable to eliminate from study those persons known not to tolerate the drug, and to use a modified double blind technique for the remaining subjects.

A saturation dive in a land-based chamber gives the constant conditions necessary to reduce the confounding effects of sudden pressure changes, motion, and immersion in water. Testing in a land-based chamber obviously will not determine efficacy against seasickness. A computerized assessment system, the Performance Measurement System (PMS), was used to look for subtle changes in diver psychomotor performance. This battery of computer administered psychomotor performance tests has been used extensively by the Navy Experimental Diving Unit (NEDU) and other diving research laboratories in the past to quantitate changes in behavior, mental performance, and psychomotor performance of divers exposed to a variety of conditions, both dry and underwater. This apparatus is described in detail elsewhere (4). Questionnaires were used to determine subjective symptoms and side effects.

METHODS

A Notice of Claimed Investigational Exemption for a New Drug was filed and accepted by the Food and Drug Administration which issued IND Number 25,580. Identical 2.5 cm² patches containing either no drug (placebo) (Lot E-11637) or a quantity of transdermal scopolamine (Lot E-11636) estimated to give a dose of 0.5 mg scopolamine over 72 hours were obtained from CIBA (Raritan Plaza III, Edison, New Jersey 08837). Ten experienced Navy divers ranging in age from 24 to 37 years, including 9 males and 1 female, participated after giving their informed consent. They took no other drugs with the exception of several participants who took multivitamins regularly. One week before the dive, all participants applied a commercial preparation of transdermal scopolamine, Transderm Scop®, for 24 hours in order to determine any pronounced unacceptable side effects. The manufacturer indicates in the package insert that the transdermal system releases an initial priming dose to bring the plasma concentration rapidly to a steady-state level, and releases scopolamine at an approximately constant rate over a three day period (Figure 2). Therefore, 24 hours appeared to be a reasonable period to observe for side effects.

The study at elevated pressures was carried out during a 6-day saturation dive in the Ocean Simulation Facility (OSF) of NEDU, which was compressed with air to a simulated depth of 60 FSW (2.8 ATA) (NEDU Test Plan Number 84-42). Neither the participants nor the diving supervisors were told which type of patch each person was wearing. All were instructed to notify the Medical Officer immediately if any serious symptoms occurred which could affect the safety of the dive. To avoid potential safety problems during critical diving operations, the schedule was arranged by the test director so that no participant entered the water (the 15 foot deep wet pot of the OSF) while wearing the active drug. All participants applied the placebo the first day and had a follow-up clinical evaluation recorded on standardized questionnaires (Figure 3). The PMS word-number test was carried out approximately 11 hours later. In this test the divers had one minute to study a slide showing six word-number pairs. For example: LOCK - 24, DREDGE - 99, etc. After one minute a second slide was displayed, this time with the same words but in a different order and without numbers. The diver's task was to recall the numbers associated with the words as shown on the second slide. At each sitting there were 2 trials of this test with different word-number pairs. The score was the number of digits remembered correctly. Immediately after testing all participants removed the patches and washed the application site. All participants applied active patches late in the evening of the second day. This was followed by questionnaires, PMS testing, and patch removal at 1:00 pm on the third dive day, 14 hours after application. Three days after the 6 day dive surfaced, a crossover study was begun, with some participants receiving the placebo and some the active drug for 24 hours followed by the same questionnaires, PMS procedures, and removal as during the dive. After 24 hours with no patch, the placebo subjects received active drug and vice versa, with the questionnaires and PMS testing repeated 24 hours later.

RESULTS

None of the diver-subjects given commercially obtained transdermal scopolamine one week before the dive had any serious side effects. Six had no side effects, 2 had mental fuzziness or mild malaise, and 3 noted dry mouth.

The symptoms reported by the diver-subjects during and after the dive are summarized in Table 1. Some diver-subjects reported more than 1 symptom so that the total number of symptoms reported exceeds the number of participants. One diver-subject was transferred to a foreign country immediately after completion of the dive and his post dive testing could not be done. The symptoms reported were obviously subjective except for pupil dilation, and none were serious enough to interfere with assigned tasks or to require removal of the patch.

Table 2 gives the results of the question on the questionnaire as to whether the patch he or she was wearing was the placebo or active patch. The criteria were highly subjective, but about half the diver-subjects correctly identified the patch they were wearing.

During the dive, one patch containing the active drug fell off after 12 hours and was reapplied by the diver-subject; one hour later it was removed and replaced by a similar new patch behind the opposite ear. No other significant problems with the patches were encountered.

Figure 4 illustrates the results of the cognitive performance testing conducted with the diver-subjects. There were no significant differences in group performance on the word-number test either as a result of pressure or of transdermal scopolamine administration. The PMS word-number test is designed to assess associative memory, or the ability to commit to memory and recall new associations. This type of test has demonstrated sensitivity to the effects of increased pressure and central nervous system changes during diving operations (5). The documented side effects of transdermal scopolamine (i.e. drowsiness, memory disturbances, disorientation and confusion) suggested that this test might also be an appropriate vehicle for quantifying the effects of these symptoms on diver performance. However, as a group there was no impaired performance at a pressure of 2.8 ATA for either the placebo or drug conditions.

Examination of individual data from the drug group at 2.8 ATA revealed that two of ten divers showed a decrease in PMS performance. Although one diver at 2.8 ATA reported "feeling fine", he scored at 64% of his baseline level on the PMS test. He also performed less well when given the drug at 1.0 ATA (71% of baseline). The second diver reported feeling "a little groggy" at 2.8 ATA, and performed at 78% of his baseline level. His performance was not impaired at 1.0 ATA. Divers who reported problems with visual focus and mental fuzziness in the drug condition at 2.8 ATA were still able to perform adequately the word-number associative memory test.

DISCUSSION

Controlled studies (1, 6) and uncontrolled reports (7, 8, 9, 10, 11, 12) describe various side effects from transdermal scopolamine. While the most common side effects are mild (e.g. dry mouth), there are occasional reports of mental changes which if present in a diver could prove as disastrous as the seasickness the drug was intended to prevent. The present study suggests that the drug may be used with safety in dry chambers at depth/pressures to 60 FSW (2.8 ATA) while breathing air. Such conditions may be found in deck decompression chambers on ships. The results of this study should not be extrapolated to predict the safe use of the drug at deeper depths where the central nervous system effects of inert gases are increased, or in the water where the effects of water on drug absorption from the patch are not known. Additional hyperbaric investigations are needed to confirm the results of the present study with a larger population and to study possible interactions of transdermal scopolamine, deeper depths, direct exposure to water, and helium oxygen atmospheres.

We originally made the hypothesis that side effects to the drug would be consistent for an individual. However, an analysis of reactions to the drug

for each diver-subject showed inconsistencies which could not be explained easily. To avoid the confounding effect of depth on side effects we compared the side effects noted during only the following three conditions: pre dive active drug, post dive active drug, and post dive placebo. Two diver-subjects had no side effects at any of these times. Two had side effects with pre dive active drug and post dive active drug, but not with post dive placebo. Three had side effects only with post dive active drug. Two had side effects with pre dive active drug and with post dive placebo, but none with post dive active drug. Of the three diver-subjects that had side effects on more than one of these conditions, there was a consistency with all three noting dry mouth; in addition, one noted fatigue with the post dive active drug.

The patches were carefully controlled and there is nothing to suggest an error in administration; so it is of great interest that two subjects given placebo complained of side effects. The mild nature of the complaints was similar to the complaints following administration of active drug.

The finding that drug-related symptoms of mental fuzziness and visual focusing problems at depth did not impair the divers' ability to process and retrieve information on the PMS test is encouraging. This suggests that the symptoms experienced were not severe or incapacitating, and that the divers could function satisfactorily in the dry chamber environment.

A prudent precaution for using transdermal scopolamine is to apply a patch for 24 hours at least several days in advance of anticipated need in those individuals who have never used the drug. The trial should be done during a time when a serious side effect would not cause safety problems. Those people who experience serious problems should not use the drug again.

SUMMARY

1. No serious side effects occurred in 10 divers using transdermal scopolamine at 60 FSW (2.8 ATA) in a dry chamber.
2. Most divers had minor side effects, with over half reporting a dry mouth.
3. Assessment of group cognitive performance showed no change due to drug or pressure.
4. In those individuals who have used transdermal scopolamine on the surface with no serious problems, dry chamber use to 60 FSW appears safe.
5. Side effects are not necessarily consistent upon repeated application of the drug.

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Table 1. Symptoms Reported by Divers as a Function of Presence of Drug And Pressure.

<u>ACTIVE DRUG</u>		
	<u>SYMPTOM</u>	<u>NUMBER</u>
PRE DIVE (1 ATA) 10 DIVERS	None	6
	Mild Malaise or Mental Fuzziness	2
	Dry Mouth or Thirst	3
60 FSW (2.8 ATA) 10 DIVERS	None	2
	Dry Mouth	8
	Mild Malaise or Mental Fuzziness	2
	Clumsiness	1
	Difficulty With Visual Focus	1
POST DIVE (1 ATA) 9 DIVERS	None	3
	Dry Mouth	5
	Drowsiness	4
	Itching at Patch Site	2
	Dilation of One Eye	1
	Difficulty With Visual Focus	1
<u>PLACEBO</u>		
	<u>SYMPTOM</u>	<u>NUMBER</u>
60 FSW (2.8 ATA) 10 DIVERS	Mental Fuzziness	1
POST DIVE (1 ATA) 9 DIVERS	Giddiness	1
	Dry Mouth	1

Table 2. Perception by Diver-Subjects On Whether They Were Wearing Active Drug or Placebo Patch

		No Opinion	Correct	Incorrect
During Dive -	ACTIVE	5	5	0
	PLACEBO	5	4	1
Post Dive -	ACTIVE	4	5	0
	PLACEBO	4	4	1



Figure 1. Transdermal Scopolamine Patch In Place Behind The Ear

Please read this instruction sheet carefully before opening the system package.

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FIGURE 2

Information for the Patient About —

Transderm® Scōp

Generic Name: scopolamine, pronounced skoe-POL-a-meen
(formerly Transderm-V)

Transdermal Therapeutic System

The Transderm Scōp system helps to prevent the nausea and vomiting of motion sickness for up to 3 days. It is an adhesive disc that you place behind your ear several hours before you travel. Wear only one disc at any time.

Be sure to wash your hands thoroughly with soap and water immediately after handling the disc, so that any drug that might get on your hands will not come into contact with your eyes.

Avoid drinking alcohol while using Transderm Scōp. Also, be careful about driving or operating any machinery while using the system because the drug might make you drowsy.

TRANSDERM SCŌP SHOULD NOT BE USED IN CHILDREN AND SHOULD BE USED WITH SPECIAL CAUTION IN THE ELDERLY.

How the Transderm Scōp System Works

A group of nerve fibers deep inside the ear helps people keep their balance. For some people, the motion of ships, airplanes, trains, automobiles, and buses increases the activity of these nerve fibers. This increased activity causes the dizziness, nausea, and vomiting of motion sickness. People may have one, some, or all of these symptoms.

Transderm Scōp contains the drug scopolamine, which helps reduce the activity of the nerve fibers in the inner ear. When a Transderm Scōp disc is placed on the skin behind one of the ears, scopolamine passes through the skin and into the bloodstream. One disc may be kept in place for 3 days if needed.

Precautions

Before using Transderm Scōp be sure to tell your doctor if you

- Are pregnant or nursing (or planning to become pregnant)
- Have glaucoma (increased pressure in the eyeball)
- Have (or have had) any metabolic, liver, or kidney disease
- Have any obstructions of the stomach or intestine
- Have trouble urinating or any bladder obstruction
- Have any skin allergy or have had a skin reaction such as a rash or redness to any drug, especially scopolamine, or chemical or food substance.

Any of these conditions could make Transderm Scōp unsuitable for you. Also tell your doctor if you are taking any other medicines.

Transderm Scōp should not be used in children. The safety of its use in children has not been determined. Children and the elderly may be particularly sensitive to the effects of scopolamine.

Side Effects

The most common side effect experienced by people using Transderm Scōp is dryness of the mouth. This occurs in about two thirds of the people. A less frequent side effect is drowsiness, which occurs in less than one sixth of the people. Temporary blurring of vision and dilation (widening) of the pupils may occur, especially if the drug is on your hands and comes in contact with the eyes. On infrequent occasions, disorientation, memory disturbances, dizziness, restlessness, hallucinations, confusion, difficulty urinating, skin rashes or redness, and dry, itchy, or red eyes have been reported. If these effects do occur, remove the disc and call your doctor. Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, be careful driving or operating any dangerous machinery, especially when you first start using the drug system.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few people following discontinuation of the Transderm Scōp System. These symptoms have occurred most often in people who have used the System for more than three days. We recommend that you consult your doctor if these symptoms occur.

How to Use Transderm Scōp

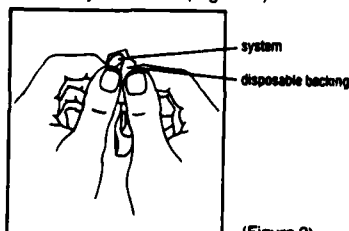
Transderm Scōp may be kept at room temperature until you are ready to use it.

1. Plan to apply one Transderm Scōp disc at least 4 hours before you need it. **Wear only one disc at any time.**
2. Select a hairless area of skin behind one ear, taking care to avoid any cuts or irritations. Wipe the area with a clean, dry tissue.
3. Peel the package open and remove the disc (Figure 1).



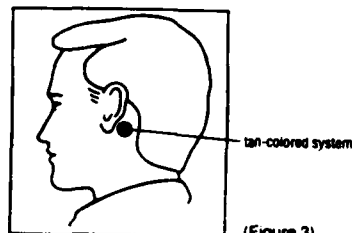
(Figure 1)

4. Remove the clear plastic six-sided backing from the round system. Try not to touch the adhesive surface on the disc with your hands (Figure 2).



(Figure 2)

5. Firmly apply the adhesive surface (metallic side) to the dry area of skin behind the ear so that the tan-colored side is showing (Figure 3). Make good contact, especially around the edge. Once you have placed the disc behind your ear, do not move it for as long as you want to use it (up to 3 days).



(Figure 3)

6. **Important:** After the disc is in place, be sure to wash your hands thoroughly with soap and water to remove any scopolamine. If this drug were to contact your eyes, it could cause temporary blurring of vision and dilation (widening) of the pupils (the dark circles in the center of your eyes). This is not serious, and your pupils should return to normal.
7. Remove the disc after 3 days and throw it away. (You may remove it sooner if you are no longer concerned about motion sickness.) After removing the disc, be sure to wash your hands and the area behind your ear thoroughly with soap and water.
8. If you wish to control nausea for longer than 3 days, remove the first disc after 3 days and place a new one *behind the other ear*, repeating instructions 2 to 7.
9. Keep the disc dry, if possible, to prevent it from falling off. Limited contact with water, however, as in bathing or swimming, will not affect the system. In the unlikely event that the disc falls off, throw it away and put a new one behind the other ear.

This leaflet presents a summary of information about Transderm Scōp. If you would like more information or if you have any questions, ask your doctor or pharmacist. A more technical leaflet is available, written for your doctor. If you would like to read the leaflet, ask your pharmacist to show you a copy. You may need the help of your doctor or pharmacist to understand some of the information.

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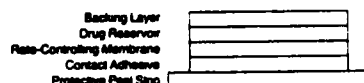
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C84-19 (Rev. 7 84)
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Transderm® Scōpscopolamine
(formerly Transderm-V)**Transdermal Therapeutic System****Programmed delivery *in vivo* of 0.5 mg of
scopolamine over 3 days****DESCRIPTION**

The Transderm Scōp system is a circular flat disc designed for continuous release of scopolamine following application to an area of intact skin on the head, behind the ear. Clinical evaluation has demonstrated that the system provides effective antiemetic and antinauseant actions when tested against motion-sickness stimuli in adults.

The Transderm Scōp system is a film 0.2 mm thick and 2.5 cm², with four layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are: (1) a backing layer of tan-colored, aluminized, polyester film; (2) a drug reservoir of scopolamine, mineral oil, and polyisobutylene; (3) a microporous polypropylene membrane that controls the rate of delivery of scopolamine from the system to the skin surface; and (4) an adhesive formulation of mineral oil, polyisobutylene, and scopolamine. A protective peel strip of siliconized polyester, which covers the adhesive layer, is removed before the system is used. The inactive components, mineral oil (12.4 mg) and polyisobutylene (11.4 mg), are not released from the system.

Cross section of the system:

Release-Rate Concept: The Transderm Scōp system contains 1.5 mg of scopolamine. The system is programmed to deliver 0.5 mg of scopolamine at an approximately constant rate to the systemic circulation over the 3-day lifetime of the system. An initial priming dose of scopolamine, released from the adhesive layer of the system, saturates the skin binding sites and rapidly brings the plasma concentration of scopolamine to the required steady-state level. A continuous controlled release of scopolamine, which flows from the drug reservoir through the rate-controlling membrane, maintains the plasma level constant.

CLINICAL PHARMACOLOGY

The sole active agent of Transderm Scōp is scopolamine, a belladonna alkaloid with well-known pharmacological properties. The drug has a long history of oral and parenteral use for central anticholinergic activity, including prophylaxis of motion sickness. The mechanism of action of scopolamine in the central nervous system (CNS) is not definitely known but may include anticholinergic effects. The ability of scopolamine to prevent motion-induced nausea is believed to be associated with inhibition of vestibular input to the CNS, which results in inhibition of the vomiting reflex. In addition, scopolamine may have a direct action on the vomiting center within the reticular formation of the brain stem. Applied to the postauricular skin, Transderm Scōp provides for a gradual release of scopolamine from an adhesive matrix of mineral oil and polyisobutylene.

INDICATIONS AND USAGE

Transderm Scōp is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The disc should be applied only to skin in the postauricular area.

Clinical Results: Transderm Scōp provides antiemetic protection within several hours following application of the disc behind the ear. In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a

FIGURE 2

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controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting. Transderm Scōp provided significantly greater protection than that obtained with oral dimenhydrinate.

CONTRAINDICATIONS

Transderm Scōp should not be used in patients with known hypersensitivity to scopolamine or any of the components of the adhesive matrix making up the therapeutic system, or in patients with glaucoma.

WARNINGS

Transderm Scōp should not be used in children and should be used with special caution in the elderly. See **PRECAUTIONS**.

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery. Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

PRECAUTIONS**General**

Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scōp should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

Information for Patients

Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the disc.

Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

Drug Interactions

Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants. **Carcinogenesis, Mutagenesis, Impairment of Fertility**

No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

Pregnancy Category C

Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect.

Transderm Scōp should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

**Transderm Scōp scopolamine
Transdermal Therapeutic System**

Nursing Mothers

It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scōp is administered to a nursing woman.

Pediatric Use

Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scōp should not be used in children because it is not known whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE REACTIONS

The most frequent adverse reaction to Transderm Scōp is dryness of the mouth. This occurs in about two thirds of the people. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of the people. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed.

The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scōp: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rashes and erythema; acute narrow-angle glaucoma; and dry, itchy, or red eyes.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few patients following discontinuation of the use of the Transderm Scōp System. These symptoms have occurred most often in patients who have used the Systems for more than three days.

OVERDOSAGE

Overdosage with scopolamine may cause disorientation, memory disturbances, dizziness, restlessness, hallucinations, or confusion. Should these symptoms occur, the Transderm Scōp disc should be immediately removed. Appropriate parasympathomimetic therapy should be initiated if these symptoms are severe.

DOSAGE AND ADMINISTRATION

Initiation of Therapy: One Transderm Scōp disc (programmed to deliver 0.5 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. Only one disc should be worn at any time.

Handling: After the disc is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal of the disc, it should be discarded, and the hands and application site washed thoroughly with soap and water and dried, to prevent any traces of scopolamine from coming into direct contact with the eyes. (A patient brochure is available.)

Continuation of Therapy: Should the disc become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. If therapy is required for longer than 3 days, the first disc should be discarded, and a fresh one placed on the hairless area behind the other ear.

HOW SUPPLIED

The Transderm Scōp system is a tan-colored disc, 2.5 cm², on a clear, oversized, hexagonal peel strip, which is removed prior to use. Each Transderm Scōp system contains 1.5 mg of scopolamine and is programmed to deliver *in vivo* 0.5 mg of scopolamine over 3 days. Transderm Scōp is available in packages of four

discs. Each disc is foil wrapped. Patient instructions are included.

1 Package (4 discs) NDC 0083-4345-04

The system should be stored at room temperature.

CAUTION.

Federal law prohibits dispensing without prescription.

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TRANSDERM-SCOP QUESTIONNAIRE

NAME: _____

DATE: _____ TIME: _____

CODE: _____

1. How do you feel?

2. Are you noticing any effects of your ear patch?

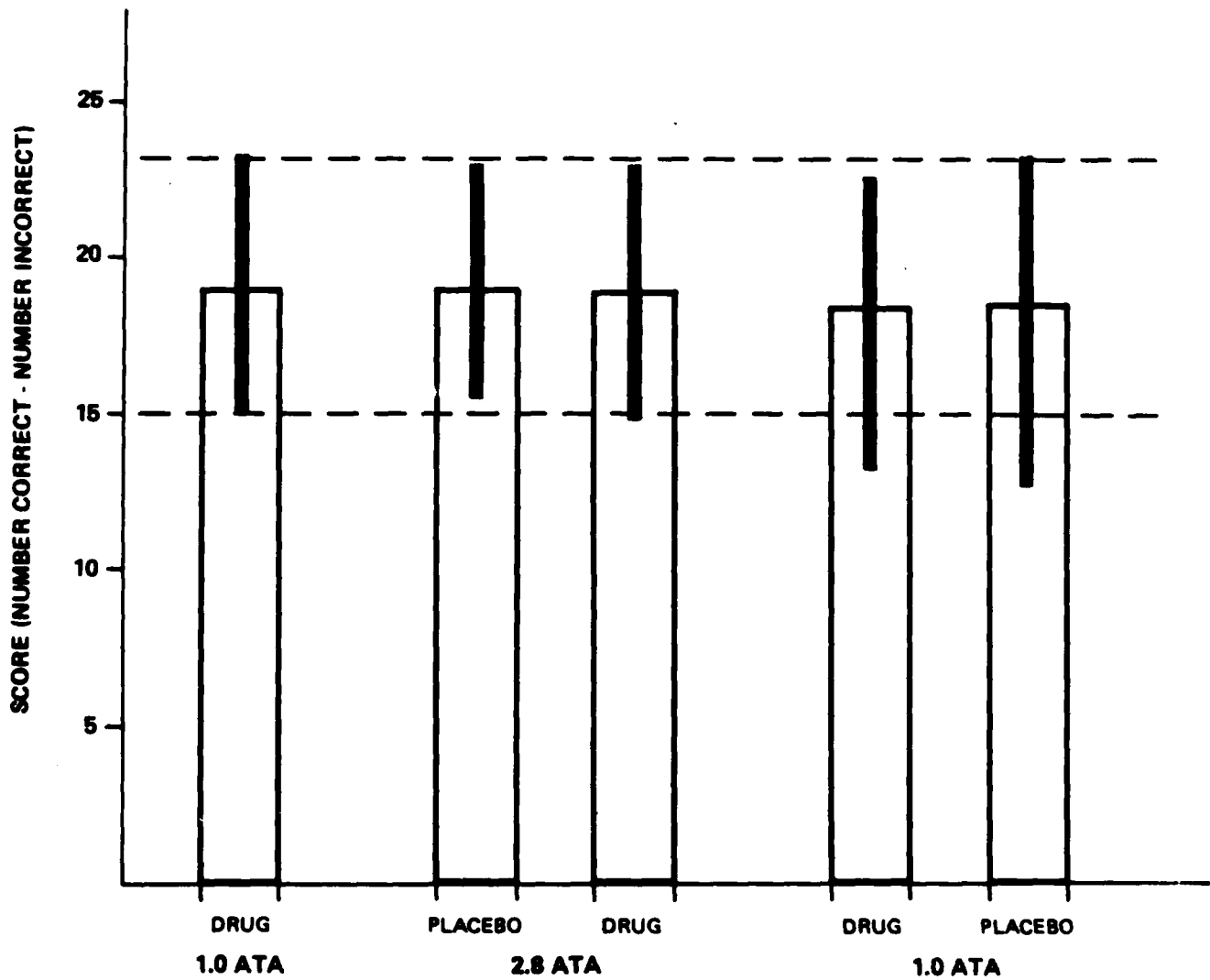
Describe. _____

3. Do you think you know which patch you are wearing? _____ Which? _____

4. Do you notice any difference between pupils in size in the mirror?

COMMENTS; Patch fell off, etc.: _____

WORD-NUMBER TEST



DRUG BY PRESSURE CONDITION

MEAN GROUP SCORES ($\pm$ 1 S.D.) ON THE PMS WORD-NUMBER TEST BY PRESSURE AND DRUG CONDITION. DASHED LINES INDICATE BASELINE PERFORMANCE OF GROUP ($\bar{x} \pm$ 1 S.D.)

FIGURE 4

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