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SUSADRIN TRANSMUCOSAL TABLETS
(Nitroglycerin in Synchron® controlled-release base)

Joseph M. Schor,[a] S.S. Davis,[b] A. Nigalaye,[a] and S. Bolton[a]

[a]Forest Laboratories (U.S.) and [b]University of Nottingham (U.K.)

Forest Laboratories has specialized in controlled-release formulations for about 25 years and has patented several systems that are in current use. In this discussion, we would like to present data on our most recently patented, third-generation system, called Synchron®, which has significant advantages over other methodologies. We will then address more specifically the concept of a buccal tablet, and give both chemical and clinical data on "Susadrin", which is a buccal tablet containing nitroglycerin, and finally, a comparison will be made between the buccal tablet and other commercial controlled-release preparations that are being used to deliver nitroglycerin to patients requiring this drug.

Synchron® is a range of polymers made from naturally-occurring materials which can be mixed directly with the active pharmaceutical substance and directly compressed into tablets. The tablets are essentially made like regular-release tablets, and, therefore, are homogeneous and reproducible on a tablet-to-tablet and batch-to-batch basis. Because of the homogeneous distribution of Synchron® and drug in the tablet, the tablet can be broken in half and still

 0363-9045/83/0907-1359$3.50/0

retain its controlled-release characteristics. This permits more accurate titration of dosage in a patient. In addition, only water, which is always present throughout the complete gastrointestinal tract, is required for the slow dissolution of Synchron®-based tablets. It is not dependent, as other systems are, on acidity, alkalinity, salts or enzymes for release as are the shallac, wax, resin and osmotic systems. Variation in these latter factors leads to variations in release rates. In short, there are no granules, cores, coatings, or waxes present and Synchron®-containing tablets cannot "dump" the drug, and do not have the poor bioavailability of certain wax systems. The Synchron® tablets are consistently reliable in releasing their active substance. The Synchron® base has very good holding power and can sustain the release of up to 10 times its weight in active drug substance.

A way of demonstrating the reliability and consistency of release from formulations containing Synchron® is to show data obtained in a human bioavailability study of Isochron, Forest's preparation of 40 mgs of the anti-anginal isosorbide dinitrate in Synchron®, versus a preparation from another company in which the 40 mgs of isosorbide is released from a granular system. These are orally-ingested, controlled-release products.

Figure 1 shows the intensity of response on the ordinate versus the time intervals at which the intensity is measured as given on the abscissa. The solid bar represents the range of response for the granular isosorbide and the hatched bar, the range of response for Forest's Isochron. The height of the bar is a measure of the variability range in response to the formulation. The greater the height of the bar, the greater the variability. Statistical analy-

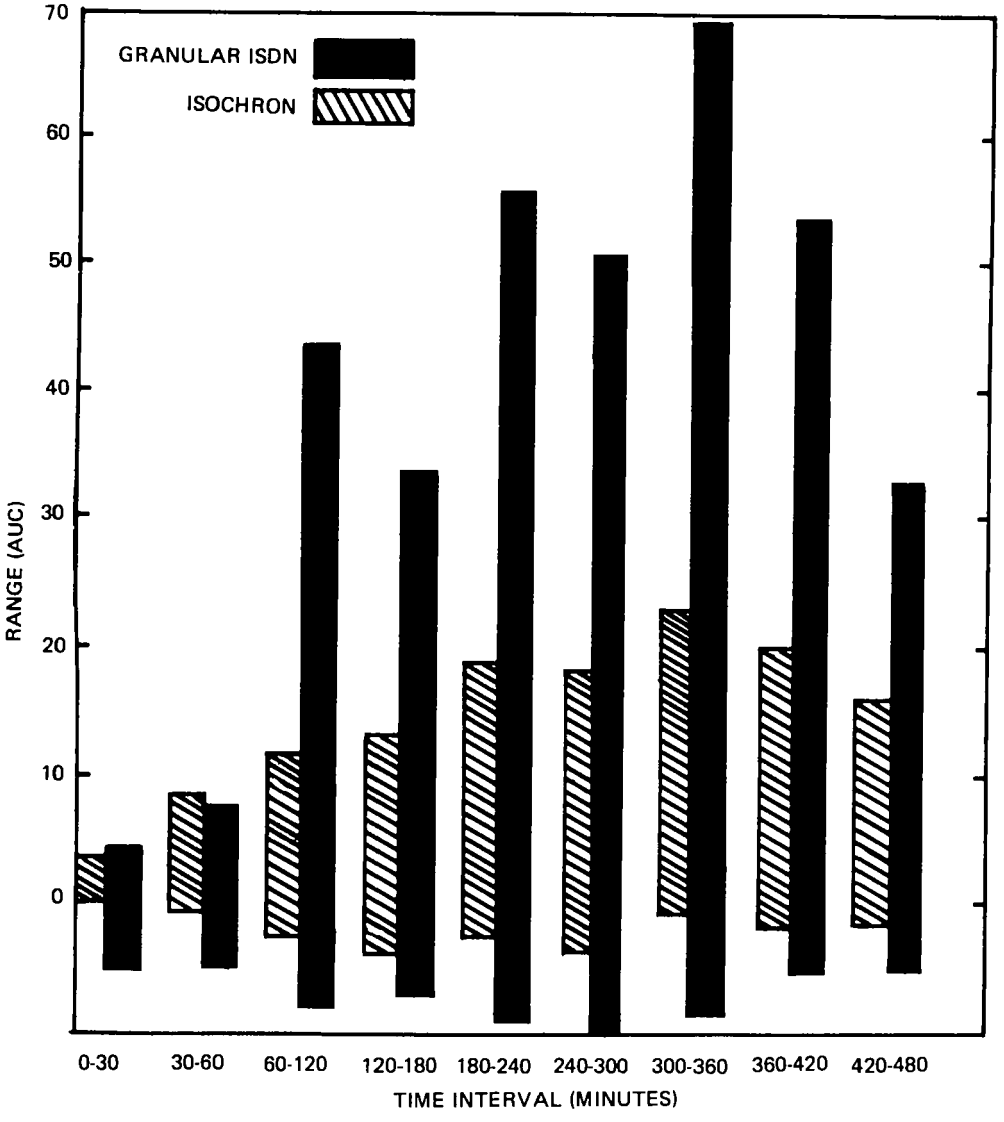

FIGURE 1

Variability Range for Area Under the Curve for Specified Intervals

sis shows the Forest's Isochron produces in humans, twelvefold less variation in response to the same quantity of isosorbide dinitrate than does the granular isosorbide sustained-release product. This means that the patient receives more consistent therapy. Thus, a Synchron®-based product shows much greater reliability and consistency than does a granular controlled-release system.

Figure 2 shows a blood level bioavailability comparison between Brocon, Forest's antihistamine decongestant in the Synchron® system, and Dimetapp, which contains the same active drug but in a wax, controlled-release system.

The ordinate gives the blood level of brompheniramine/ml plasma (brompheniramine is one of the major active components in Brocon). The abscissa gives the time in hours over which the blood level measurements are made. It can be seen that the area under the Brocon curve is much larger than the area under the Dimetapp curve. The area under the curve shows that the bioavailability from the Forest Brocon is approximately twice that from the Dimetapp. Thus, Synchron®-containing formulations have excellent bioavailability in addition to the greater consistency, reliability, and reproducibility that has already been discussed.[1]

Nitroglycerin is a drug that has been used for over 100 years to relieve the pain of angina pectoris, but its delivery to the patient in order to achieve this effect has been a difficult problem primarily because of its instability and the very rapid and extensive destruction by first-pass liver metabolism. Therefore, relatively large doses must be given orally and this is sometimes associated with side effects such as headache.

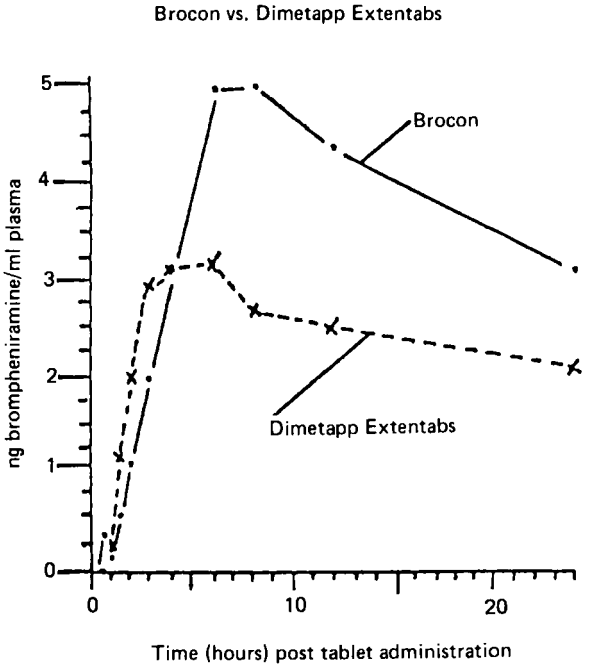

FIGURE 2

Plot of mean brompheniramine plasma levels following Brocon® tablet administration vs. Dimetapp Extentabs® tablet administration.

Many routes of delivery have been used, such as sublingual, intravenous, transdermal, and buccal, i.e., the oral transmucosal route.

The intravenous route, although effectively delivering the nitroglycerin, is inconvenient and carries with it liabilities common to intravenous dosing. The ointment route is effective if sufficient ointment is utilized, but the duration and convenience remain a problem. The transdermal or patch route has severe limitations because the skin is designed by nature to prevent absorption of substances and this will be discussed later. The sublingual route is quite effective in delivering the drug and is the "gold standard" but acti-

vity is short-lived -- of the order of minutes -- and this route cannot be used for sustained release of nitroglycerin, i.e., for chronic prophylaxis. However, the buccal route has all the advantages of the sublingual route in that the buccal mucosal tissue is similar to sublingual mucosa and is designed by nature for ease and rapidity of absorption, and additionally, permits the prolonged holding in the lip or cheek pouch of a controlled-release tablet for the hours required for acute and chronic prophylaxis of angina.

Beckett et al,[2] have studied the oral mucosal absorption of a number of drugs using a technique which consisted of placing a drug solution in the mouth for a 5 minute period and then expelling and collecting the residual contents of the mouth. The amount of drug presumably absorbed through the mucosa is the difference between the amount placed in the mouth and the amount in the fluid expelled. Unfortunately, rinses of the mouth contained relatively large quantities of the supposedly absorbed drug.

We have used a more modern approach in investigating absorption by the buccal route; namely, the use of external gamma scintigraphy,[3] to monitor the release of a gamma-emitting radionuclide 99^{m} technetium which has been incorporated into a buccal tablet made with Synchron®. The tablets were given to healthy male volunteers. The subjects were seated with the face positioned against the collimator of the gamma camera and the activity, i.e., the counts versus time, profile recorded. Each subject acted as his own control and was also given sublingual, immediate-release tablets in which the technetium was incorporated. The release profile of the Synchron® buccal tablet approximates to a linear relationship between the percentage of activity remaining in the tablet and time, i.e., zero order kine-

tics. This can be seen in Figure 3. The rapidity of release of technetium from the sublingual tablet can also be observed. It is, therefore, apparent that Synchron® can be used to produce controlled-release buccal tablets that will slowly release active material with zero order kinetics.

This knowledge of the characteristics of Synchron® was used in the development of Susadrin which is a buccal tablet of nitroglycerin in Synchron® controlled-release base. Susadrin is the first sustained-release nitroglycerin tablet for easy and unobtrusive absorption through the profuse capillary system contained in the mucosal membranes of the gum and inside cheek lining and thence directly into the systemic circulation. The tablet was designed to achieve the well-recognized rapid onset of action and high potency of sublingual nitroglycerin, and to prolong that effect for up to six hours.

The buccal tablet is quite small and one of its inherent characteristics is that it will adhere to the buccal mucosa and not require adhesives to hold it in place. Also, it cannot be duplicated with granular sustained-release technology because one would end up with a mouthful of small granules. The buccal tablet is so unobtrusive that the patient forgets that he has the tablet in place and it cannot be noticed from an external viewpoint. The patient may talk, drink and even eat with the tablet in place. If, occasionally, a crust of bread dislodges the tablet and it is swallowed, there will be no adverse consequences because the first pass liver metabolism will inactivate the small amount of nitroglycerin present. The patient can simply put another tablet into his buccal pouch. The tablet completely dissolves over a period of hours to produce a steady high

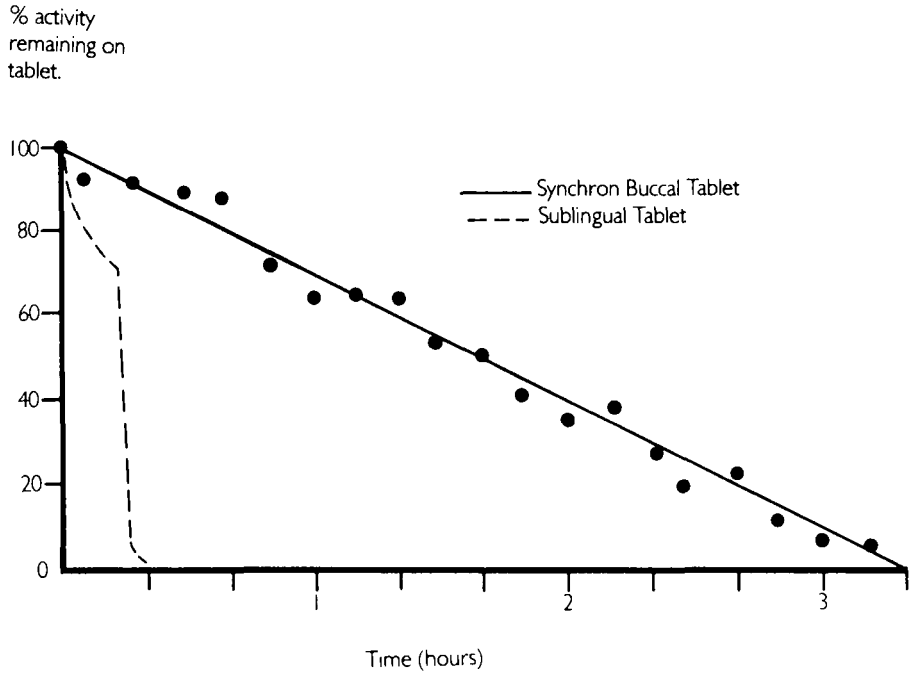

FIGURE 3

Release of 99m-Tc DTPA from Synchron Buccal Tablets (Suscard) and from sublingual tablets

level of clinical activity over a period of 5 to 6 hours. Because there is almost no inactivation of the nitroglycerin by first pass liver metabolism and the efficiency of the absorption is high, only relatively small amounts of nitroglycerin, of the order of 1 to 5 mgs, are needed to produce intense, prolonged levels of activity.

A unique feature of Susadrin is the stability that Synchron® provides to nitroglycerin, which is highly volatile material. It is well known that sublingual nitroglycerin tablets will lose potency very rapidly once dispensed. Susadrin tablets, however, have a three year shelf-life at room temperature, which frees the patient from worry about whether his tablets are still active. Figure 4

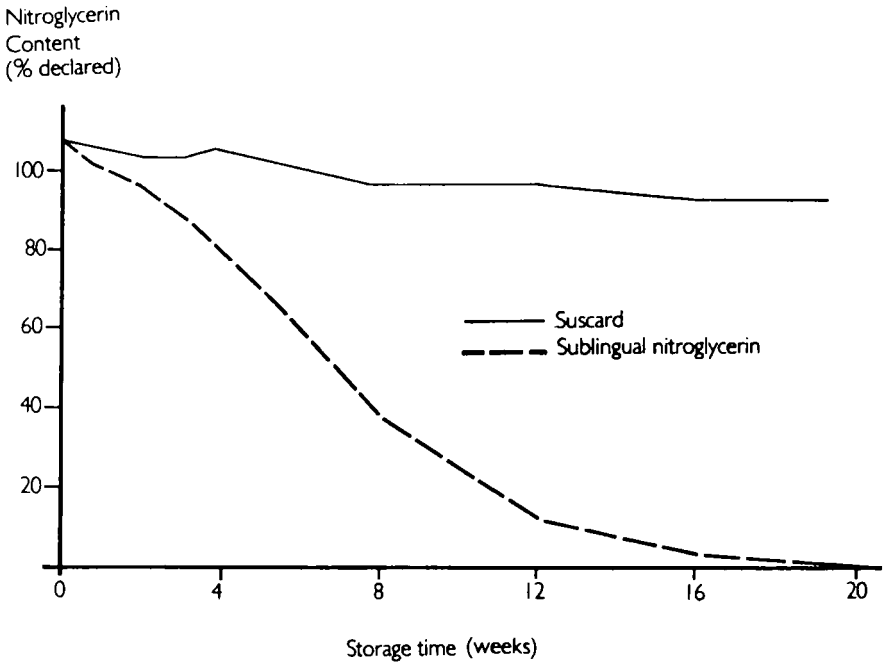

FIGURE 4

Nitroglycerin content of tablets stored at room temperature in open containers.

shows the nitroglycerin content of Susadrin tablets, and sublingual nitroglycerin tablets versus time; both products were stored in open containers at room temperature. It can be observed that the nitroglycerin content of the sublingual tablet falls sharply over a 12 week period, whereas the Susadrin has retained essentially all of its potency.[4]

Figure 5 shows the DPG bioavailability of nitroglycerin from Susadrin. A 0.6 mg sublingual dose of nitroglycerin serves as a positive control. It may be observed that the intensity of the response for the buccal tablet is at least as great as that of the 0.6 mg sublingual; that the duration of potent levels covers a 5 hour period; and that the onset of activity is as rapid as that producted by the sublingual preparation.[5]

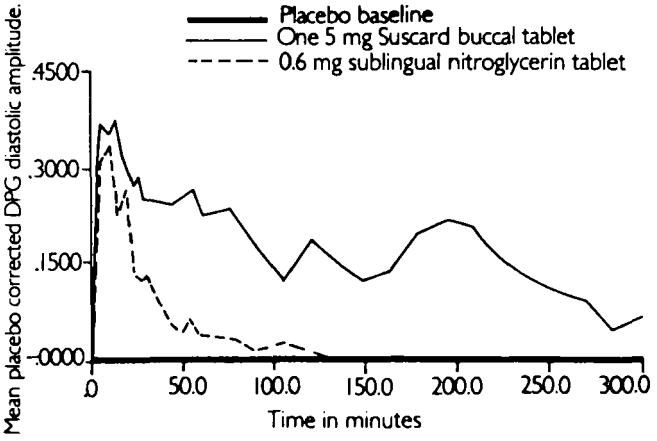

FIGURE 5

Placebo-corrected Digital Plethysmographic (DPG) response for 5.0 mg buccal nitroglycerin tablets, and for 0.6 mg sublingual nitroglycerin.

Clinical test of Susadrin have been conducted in angina patients, using a double blind, crossover exercise tolerance protocol, developed at the National Institutes of Health. This is the most rigorous, definitive means of assessing anti-anginal activity. This protocol consists of exercising the patient at increasing work loads on a bicycle and timing the onset of angina. If the patient is given nitroglycerin and exercised, it has been found that he can exercise for longer periods of time before developing angina. This relates to the real-life situation because the patient can do more activity before reaching the point of developing an anginal attack. The first study, rigidly controlled by Dr. Nathaniel Reichek[6] at the University of Pennsylvania Medical School, and a second, confirmatory study conducted by Dr. Edgar Lichstein[7] at Maimonides Hospital in Brooklyn, have demonstrated clearly the great effectiveness of Susadrin in increasing the exercise tolerance of moderately

to severely ill angina patients or even in abolishing the angina completely.

Figure 6 shows the exercise tolerance data in patients with the tablet in place. The Y axis shows the exercise tolerance time and the X axis gives the hours over which the patients were repetitively exercised. The large increase in exercise tolerance time of over 50%, occurring over a 5 to 6 hour period, can clearly be seen, but of special note is the fact that the exercise tolerance improvement showed great linearity. These are extraordinary results, but in reality the results are even better than indicated because approximately 44% of all the exercise tests ended in fatigue rather than angina; that is, angina could not be induced in these patients because of the strong effect of the nitroglycerin. If angina could have been induced in these patients, the exercise tolerance time would have been greater.

To further confirm the great potency of Susadrin, it can be seen from Figure 7, where a comparison is given of mean exercise performance on sublingual and buccal nitroglycerin in patients to whom these dosage forms were administered on separate occasions. The improvement in performance over a full 5 hour period following administration of Susadrin is comparable to that recorded five minutes after administration of sublingual nitroglycerin when it is at its peak effect. This linearity of the high potency is another example of zero order kinetics and allows the conclusion that Susadrin functions as a long-acting sublingual nitroglycerin preparation even though it is not placed under the tongue.

Open, chronic-dosing, clinical studies in anginal patients, conducted by Drs. Reichek and Lichstein, have demonstrated that

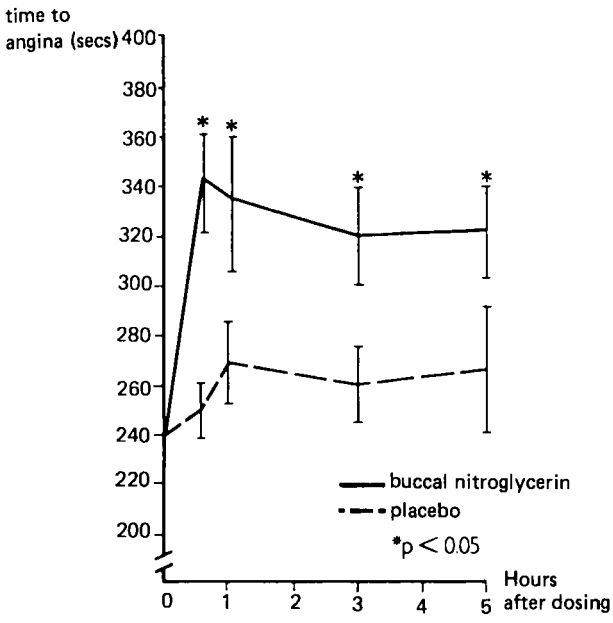

FIGURE 6

Exercise tolerance in patients in whom the buccal tablet was still present after 5 hours.

approximately 50% of the patients become totally angina free when they take Susadrin and the remainder were substantially improved. This correlates well with the closed, exercise tolerance studies of these two investigators. Two large multicenter studies in the United States and one in the United Kingdom confirm the statistics and findings of Drs. Reichek and Lichstein.

When one discusses the treatment and prophylaxis or prevention of angina, there are three prime indications for use of nitroglycerin. We have just discussed one of them, i.e., the use of nitroglycerin for the prophylaxis of chronic angina when the patient must have nitrate coverage for at least all of his waking hours, which includes about 90% of all chronic anginal pain. The open,

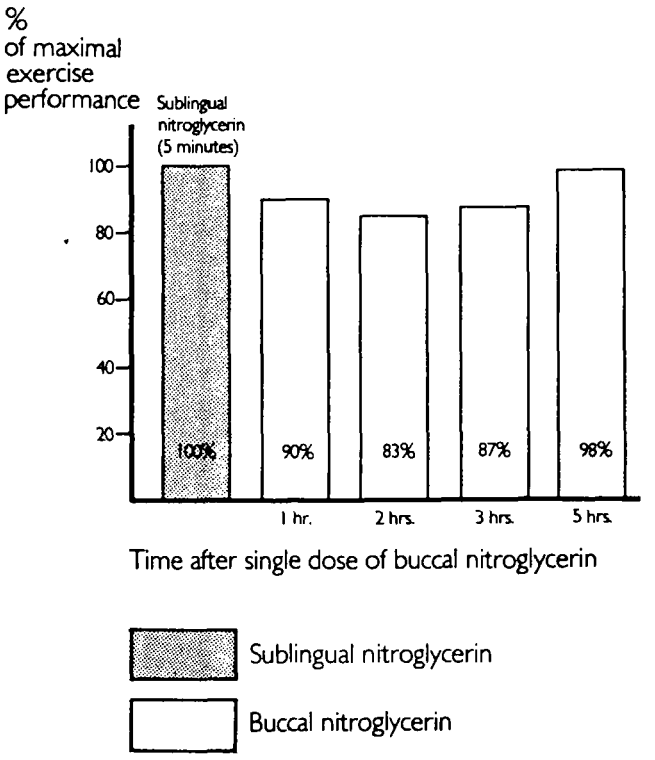

FIGURE 7

Mean exercise performance; sublingual and buccal nitroglycerin.

chronic-dosing studies just discussed have shown that three-times-a-day dosing with Susadrin on a chronic basis will result in at least 50% of the patients achieving complete freedom from anginal pain, a level not heretofore observed with any medication for angina.

A second indication is the use for acute or short-term prophylaxis where the patient knows that a particular type of emotional or physical stress such as tennis, walking, mowing or sex will induce an attack of angina. In anticipation of the stressful situation, the patient merely has to place a transmucosal Susadrin tablet in his buccal cavity and protection from angina will ensue immediately.

After the stressful situation is over, the patient has the option of removing the buccal tablet.

A third anti-anginal indication is the actual treatment of an anginal attack which is in progress; that is, aborting an attack in progress. Sublingual nitroglycerin is the standard treatment for this situation because of the rapidity of onset of activity and its great potency. The comparability of Susadrin to the sublingual tablet was investigated in a study in anginal patients who were catheterized, and the decrease in pulmonary blood pressure was determined by Dr. Langbehn[8] of the Bad Segeburg Clinic; results are given in Figure 8. Dr. Langbehn found that statistically significant activity was obtained within 60 seconds of dosing with Susadrin and was indistinguishable from the sublingual nitroglycerin preparation. In fact, pulmonary artery systolic pressure, under the influence of the buccal preparation, had decreased significantly within 30 seconds. This study, therefore, clearly demonstrated that Susadrin acts as rapidly and with the same potency as sublingual nitroglycerin. Dr. Reichek has studied the decrease in left ventricular end-diastolic pressure and found the decrease to be rapid and indistinguishable from that induced by sublingual nitroglycerin. Thus, Susadrin has a speed and potency of action comparable to sublingual nitroglycerin and should be useful to abort an anginal attack.

We would like to present now some comparative data with other nitroglycerin products. Figure 9 shows the time to peak plasma level on the X axis and the peak plasma nitroglycerin levels at that time on the Y axis. It can be seen that Susadrin and sublingual nitroglycerin give approximately the same plasma levels at 4 minutes after dosing and that at 10 minutes, the Susadrin gives very high

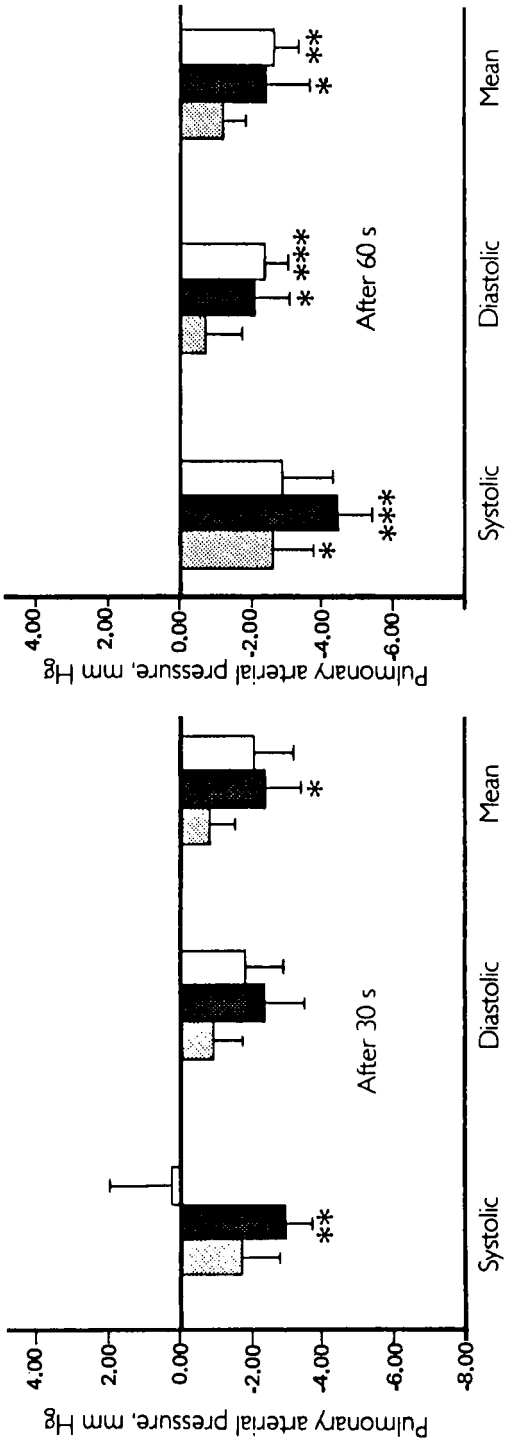

FIGURE 8

Changes in pulmonary artery pressure, 30, 60 and 120 seconds after administration of buccal & sublingual nitroglycerin.

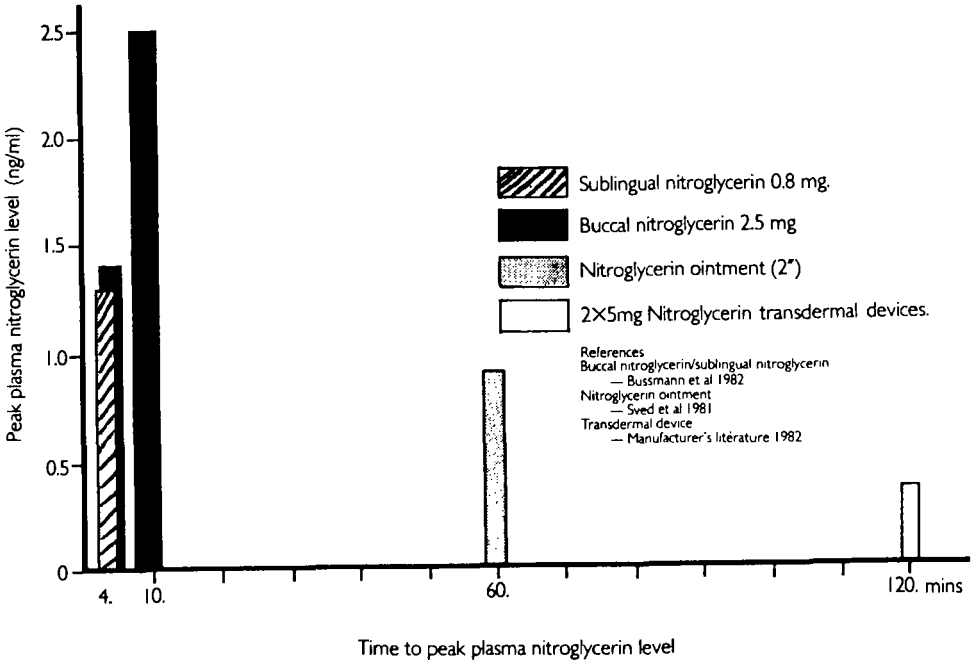

FIGURE 9

Peak plasma nitroglycerin level, and time taken to attain peak level for nitroglycerin dosage forms.

blood levels of 2.5 nanograms/ml; two inches of nitroglycerin ointment or paste give a peak level of about 0.8 nanograms/ml 60 minutes after application. Twenty square centimeters of the Ciba-Geigy[9] patch produce a peak level of about 0.3 nanograms/ml as do the Searle and Key patches. This is the same level that 0.5 inches of nitroglycerin ointment induces. This is not considered a therapeutic dose because the dose of ointment usually given is one to two inches, with a mean of one and one-half inches, and it would require about 6 patches to reach the effectiveness of one and one-half inches of ointment. It would appear, therefore, that the patch probably has, at best, only weak activity. In short, the data show clearly the very superior blood levels and rapidity of onset of Susadrin compared to the patch and ointment.

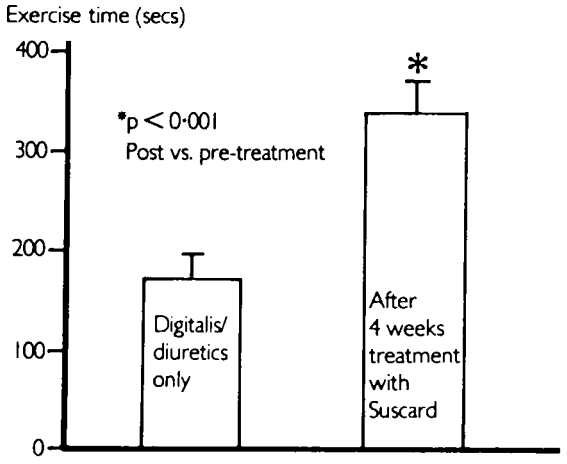

FIGURE 10

Exercise tolerance in patients with congestive cardiac failure.

In addition to its usefulness in treating angina, nitroglycerin has been found to be effective in the treatment of congestive heart failure when it is given by the intravenous route of administration. The effectiveness of nitroglycerin when given by oral ingestion or by sublingual administration has not been established because these preparations cannot provide the sustained high levels of nitroglycerin required to treat this disease entity. However, Dr. Lahiri[10], at Northwick Park Hospital in the United Kingdom, has been able to show that chronic dosing with the 5 mg Susadrin tablet results in a marked increase in exercise tolerance time in congestive failure patients as shown in Figure 10. Dr. Lahiri's results have been reported in the British Medical Journal.

In summary, the transmucosal route of absorption is very efficient because the mucosa, i.e., gums and inside cheek surfaces,

are rich in capillaries and are, in fact, excellent absorbing surfaces in contradistinction to skin which is designed to prevent absorption of most materials into the body. The transmucosal absorption is so rapid and efficient it is very similar to an intravenous infusion but without the necessity of a needle.

Data has been presented showing the usefulness of Susadrin for acute and chronic prophylaxis of angina. It is also useful for aborting an anginal attack because of its comparability to a sublingual tablet with respect to time of onset and potency. Susadrin functions as if it were a long-acting sublingual tablet.

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