

Evaluation of a Noninvasive Automatic Continuous Systolic Blood Pressure Monitor and a Noninvasive Deep Body Thermometer for Clinical Trials

— Comparison of Three Acute Hypotension Cases —

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(Received on 24 August 1979)

Summary

An automatic continuous systolic blood pressure monitor (Shimazu SCS-501) and a deep body thermometer (Terumo finer core temp DC-1) were used to observe hemodynamic changes induced by thymoxamine hydrochloride, FK 749, and hemodialysis. Three acute hypotension cases were observed in these studies.

By means of SCS-501, DC-1, and a sphygmomanometer, it was suggested that the acute hypotension cases differed from each other. From these observations the authors concluded that the combined use of SCS-501 and DC-1 with an ordinary sphygmomanometer gives them detailed information about hemodynamic changes and that both pieces of equipment will be very useful in estimating the safety and effects of drugs.

Key Words : New equipments in clinical trials, Noninvasive methods, Analysis of acute hypotension cases

Introduction

For the evaluation of drug effect and safety in healthy subjects, noninvasive methods are recommended as monitors. This is because they have the advantages of causing no pain, the anxiety, discomfort, or danger in comparison with the standard invasive methods, and thus can be used for repeated or prolonged studies in normal subjects or patients. Continuous records are favored in the accurate evaluation of drug-induced hemodynamic changes because inter-

mittent records occasionally fail to note the acute or short-lasting effects of drugs.

In the present study, an automatic continuous systolic blood pressure monitor (Shimazu SCS-501) and a deep body thermometer (Terumo finer core temp DC-1) were used in both normal subjects who were administered a new drug and patients under hemodialysis for continuous measurement of the systolic blood pressure (S. B. P.) and deep body temperature (D. B. T.), which may be reflective of the tissue blood flow.

Three types of acute hypotension observed during this study were analysed by this equipment, and the data gained thereby was also compared with the changes observed by using an ordinary sphygmomanometer. The usefulness and advantages of these monitors will be discussed.

Methods

SCS-501 is a machine used in the continuous, noninvasive measurement of the S. B. P. first produced by Man-i et al. (1977). Two types of detectors are available. One is an earpiece-type detector and the other is a fingertip-type detector. DC-1 is used for the continuous, noninvasive measurement of the D. B. T. It was devised by Fox and Solman et al. (1973) and improved by Togawa (1976). SCS-501 and DC-1 were applied in three clinical trials.

1. Thymoxamine hydrochloride at 10 mg administered by single intravenous injections (i. v.) over a 5 minute period :

Three healthy male subjects (ages 24-30, mean age 27 years) took part in this study. The procedures involved in study and its associated hazards were fully explained, and written consent was obtained from each subject.

2. FK 749 (a cepharosporin derivative produced by Fujisawa Pharmaceutical Company) at 2000 mg, i. v. over a 1 minute period :

6 healthy male subjects (ages 30-40 years, mean age 37 years) took part in this study after giving written consent.

3. Hemodialysis :

6 patients (ages 24-50, mean age 34 years) were monitored with the equipment during hemodialysis after giving oral consent.

All experiments were carried out under identical conditions in an air-conditioned room at $22 \pm 1^\circ\text{C}$. The subjects were placed in supine

position at rest on an examination bed, and following parameters were continuously monitored for the whole period of each study. About 1 hr was required for the temperature to reach equilibrium. The detector of SCS-501 was attached to the ear or fingertip of the right hand, after which the S. B. P. and pulse rate were recorded continuously. The detector of DC-1 were attached to the forehead, the palm of the right hand, and the sole of the foot. The skin temperature of the finger cushion was also measured continuously. Finally, the upper arm blood pressure was also measured by a sphygmomanometer at 15 min intervals.

Results

1. Thymoxamine hydrochloride at 10 mg i. v.

The S. B. P. decreased gradually with no change in the pulse rate. The D. B. T. of the palm and skin temperature transiently fell and then elevated remarkably, while the D. B. T. of the sole elevated (Nakashima et al., 1979).

One of the subjects felt abdominal peristalsis and warmth and broke into a cold sweat at the time of taking the blood sample 20 min after administration of the drug. The blood pressure taken by sphygmomanometer on the upper arm fell from 102/50 to 75/32, recovering within 2-3 min. The S. B. P. of the fingertip fell rapidly with its recovery time taking about 50 min. The D. B. T. and the skin temperature also fell. However, the temperature recovered within about 15 min. Fig. 1, 2 show the changes of the S. B. P., pulse rate, and body temperature.

2. FK 749 at 2000 mg, i. v.

Five of the six volunteers did not show any remarkable change. The sixth complained of nausea and abdominal discomfort during the

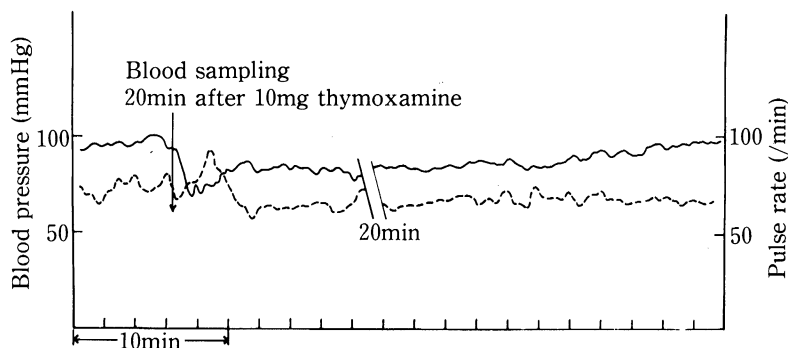


Fig. 1 "Acute hypotension" observed after thymoxamine at 10 mg, i. v.—: systolic blood pressure. ---: pulse rate

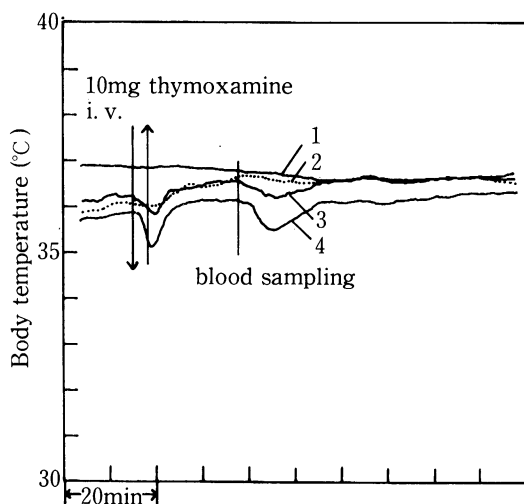


Fig. 2 The effect of thymoxamine at 10 mg, i. v. on body temperature. 1: forehead D.B.T. 2: sole D.B.T. 3: palm D.B.T. 4: fingertip skin temperature

injection. The S. B. P. fell transiently and the change was accompanied by an increase in pulse rate. However, the subject recovered within 1 min following completion of the injection. The change in blood pressure taken on the upper arm was too short to be observed. In this subject, similar changes of the S. B. P. and pulse rate were also observed at the time of blood sampling (Fig. 3).

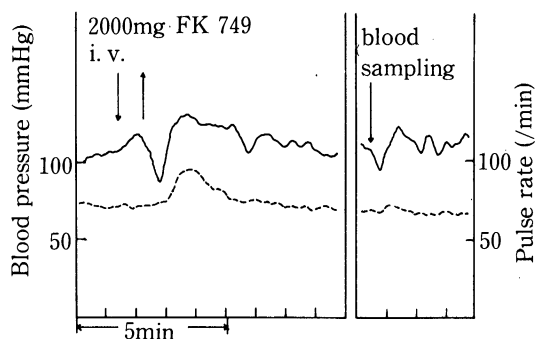


Fig. 3 The effect of FK 749 at 2000 mg, i. v. (left panel) and blood sampling (right panel) on systolic blood pressure and pulse rate. —: systolic blood pressure, ---: pulse rate

3. Hemodialysis

In these patients, the attachment of the fingertip detector proved very difficult, and so the earpiece detector was used. The D. B. T. did not change in any of the patients. One patient became acutely hypotensive 1.5 hours after the start of the hemodialysis. Fig. 4 shows the changes in the S. B. P. and pulse rate in this patient. The S. B. P. gradually lowered, the pulse rate increased, and thereafter the S. B. P. and pulse rate fell simultaneously and the patient lost consciousness. An injection of 100 ml of physiological saline had no effect, but supriphen (Carnigen®) elevated the S. B. P. The body tempe-

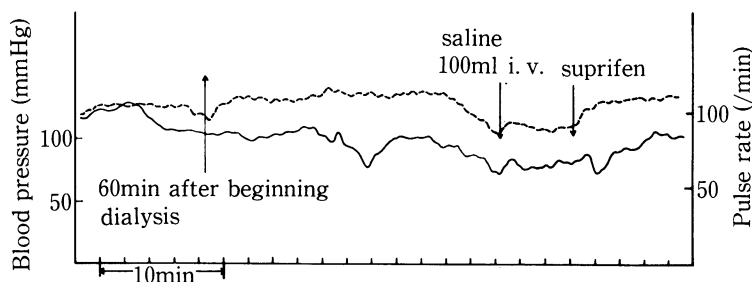


Fig. 4 "Acute hypotension" observed during renal dialysis. — : systolic blood pressure, --- : pulse rate

rature showed no change.

Discussion

According to Man-i et al. (1977), the value measured by SCS-501 is different from and lower than that measured on the upper arm by the ordinary sphygmomanometer or the invasive method with a catheter. However, there is a good correlation between both values. Therefore, we used SCS-501 to continuously observe relative changes in the S. B. P.

Measurement of the D. B. T. is hardly affected by the air temperature (Kobayashi et al., 1975). The D. B. T. at several points on the body can be measured with DC-1 safely and without pain for several hours. As blood is thermal carrier, the D. B. T. may reflect tissue blood flow. So DC-1 gives some information about tissue blood flow that could not be obtained with an ordinary surface thermometer. The forehead D. B. T. is lower by $0.4\sim 0.9^{\circ}\text{C}$ than the rectal temperature, but it is possible to substitute forehead D. B. T. for rectal temperature as the central temperature (Tsuji, 1976). Peripheral D. B. T. at the palm and sole changes rhythmically, with the changes of the palm D. B. T. being more remarkable and rapid than those in the sole. The temperature of the skin of the fingertip changes delicately, but is easily

affected by the air temperature (Tsuji 1976).

Thymoxamine hydrochloride has α -blocking action (Birmingham and Szolesnyi, 1965, Arbab and Turner, 1970) and has been used in Europe in the treatment of hypertension (Mosler, 1960), cerebrovascular insufficiency (Aleksic, 1961), asthma bronchiale (Alston and Patel, 1974), and glaucoma (Mayer et al., 1977). In Japan, however, it has never been used in humans. The initial changes of temperature observed during the injection of thymoxamine (Fig. 2) may have been caused by pain. Thymoxamine lowered the S. B. P. and elevated the sole and palm D. B. T. as well as the skin temperature at the finger tip. But the forehead D. B. T. did not elevate, indicating the central temperature did not change. These changes suggested that thymoxamine induced dilatation of the peripheral vascular bed.

In the present study, three types of hypotension were observed using SCS-501. The changes observed with SCS-501, a sphygmomanometer, and DC-1 during these acute hypotension cases are summarized in Table 1. The first was observed after thymoxamine injection, the second was induced by FK 749 injection, and the last occurred during renal dialysis. In the first case, the blood pressure measured by the ordinary sphygmomanometer fell and recovered

Table 1 Three Types of Acute Hypotension Observed in this Study

Monitor	Blood pressure		Body temperature
	SCS-501	Sphygmomanometer	DC-1
Treatment	↓↓ (long)		
I, Thymoxamine	↓ (short)	↓↓ (short)	↓ (long)
II, FK749	↓ (short)	—	—
III, Renal dialysis	↓↓ (long)	↓↓ (long)	—

↓ : fall ↓↓ : remarkable fall

— : no change () : duration

short : less than 15 min long : 15~60 min

within 2–3 min, but the fall of the systolic blood pressure recorded with SCS-501 continued for 50 min, indicating that recovery from acute hypotension in central compartment was rapid while it was more sluggish in the peripheral region. In the second case, the hypotension was not observed by the ordinary sphygmomanometer nor was any change recorded by DC-1, suggesting that the change was transient and may have been caused by nervous reflex. In the last case, the hypotension was caused by the decrease in blood volume. The change in blood pressure recorded by SCS-501 was similar to that measured with the sphygmomanometer, indicating that this hypotension differed from other two cases. Attachment of SCS-501's fingertip detector proved very difficult and DC-1 recorded no change, suggesting that the change in blood flow in the finger was undetectable because the blood vessel had already been restricted due to surgical operations on the internal or external arteriovenous shunt. Injection of physiological saline produced no change, but supriphen was effective. Cardiogenic factors may have been involved in this case.

From these observations we concluded that the combined use of these two tools with an ordinary sphygmomanometer gave us detailed information about hemodynamic changes.

These two tools have following advantages : 1) they are noninvasive methods, and therefore are harmless and do not cause pain ; 2) they allow for repeated or relatively prolonged studies in both normal subjects and patients ; 3) the continuous recording gives information of relatively greater detail for the evaluation of drugs ; 4) combined use of these tools with the ordinary sphygmomanometer permits accurate evaluation of drug-induced hemodynamic changes.

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