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ABUSE AND PARADOXICAL EFFECTS OF ANALGESIC DRUG MIXTURES

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1 In patients with chronic pain, two types of analgesic drug dependence occur, that is, dependence of the barbiturate-type and of the morphine-type. Eighty cases of analgesic drug dependence of the barbiturate-type were examined. All these patients were dependent on drug combinations, not a single patient being on one analgesic alone.

2 Psychotropic agents were found to be the common pharmacological denominator of all abused preparations. These findings confirm the hypothesis that the addition of psychotropic or dependence-producing substances to analgesics is the crucial factor in the complex of mild analgesic drug abuse.

3 One group of patients with chronic pain, who were dependent on analgesic drug mixtures, had both lowered experimental pain thresholds and tolerances. After drug withdrawal, these parameters showed a tendency to increase in some patients.

Introduction

In patients with chronic pain, two types of drug dependence occur, namely drug dependence of the barbiturate-type and of the morphine-type according to the classification of the WHO (Eddy, Halbach, Isbell & Seevers, 1965). A minority of pain patients with multiple drug abuse become dependent on both types (Wörz & Gerbershagen, 1978). This report deals with personal observations of 80 patients, who were dependent on non-narcotic analgesic drugs.

Methods

In all cases the original motive to take analgesics was the presence of pain. No patient belonged to the so-called drug scene. The age range was 20–71 yr, (median 45.5 yr). We examined 38 cases (23 female, 15 male) in our outpatient pain clinic and 42 women inpatients with longstanding headaches. Therefore we do not claim that this is a representative sample, either in the sex ratio or the distribution of different underlying pain syndromes.

Thirty patients with pain and with dependence of the barbiturate-type, who were informed of our investigations, participated voluntarily in algometric tests. One group (A) of 15 individuals (10 female, 5 male) were compared with 15 healthy volunteers. The age range (group A) was 27–63 yr (median 45 yr). They had complained of severe, continuous headaches (8), facial pain (1), back pain (1), pain after amputation (1), and multiple pain syndromes (4) for 1–27 yr (median 10 yr). These patients estimated the duration of their dependence from 4 months to 25 yr (median 8 yr).

The age range of the healthy volunteers (10 female, 5 male) was 22–56 yr (median 39 yr). They were employees (9) of our hospital, nurses (3), male nurses (2), and one physician.

Another group (B) of 15 chronic pain patients (10 female, 5 male), who were dependent on non-narcotic analgesic combinations had an age range of 25-67 yr (median 43 yr). They suffered from persistent headaches (11), facial pain (1), low back pain (2), and multiple pain syndromes (1). These patients estimated the length of their dependence from 1–50 yr (median 5 yr). The algometric values for group B were compared with those of 15 patients (10 female, 5 male) with similar pain syndromes, but without analgesic drug abuse (group C). These patients suffered from severe chronic headaches (10), facial pain (1), low back pain (2), and multiple pain syndromes (2). Their pressure pain thresholds, measured on the forehead, were compared with those of group B.

Four algometric tests were used to determine 'pain threshold' and 'pain tolerance'. Pressure was applied on the forehead and on the left tibia. The area of contact was 385 mm^2. Pain was also induced with a sphygmomanometer cuff on the calf. Every 2 s the pressure was increased by 10 mm Hg.

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Apart from this, radiant heat was produced using a modification of the 'dolorimeter' of Hardy, Wolff & Goodell (1952) and directed on a forearm, blackened with Indian ink. The radiant heat at the measuring tube of our instrument (area 3.45 cm^2), which uses a 100 W lamp, was empirically determined through preliminary calorimetric examinations to be 1.863 Joule/second.

After a demonstration trial, the participants defined the beginning of pain ('pain threshold') with "now" and "intolerable pain" ('pain tolerance') with "stop". In all experiments the mean of three results was used. In the pressure tests, results were registered in kiloponds, with the sphygmomanometer cuff, in mm Hg; and in the heat tests, the radiation periods were recorded to 0.1 s and converted into Joules.

Results

All 80 patients were dependent on fixed drug combinations; 26 were multiple drug abusers and 54 took one or only a few preparations regularly. All these chronic pain patients had both psychic and physical dependence of the barbiturate-type, as defined by Eddy *et al.* (1965). Usually, abstinence-symptoms began the first day after discontinuation of the drugs, reaching a climax on the second or third day and decreasing after a few days. The exacerbation of pain intensity after cessation of drugs is a prominent feature of this kind of abstinence-syndrome in chronic pain patients.

However, 3–4 d afterwards, a few patients said spontaneously that they were pain-free for the first time for years. The majority of patients reported an improvement. In rare cases, the signs and symptoms of withdrawal continued longer than 1 month. The abstinence-syndrome showed all degrees of intensity from slight restlessness or sleep disturbances to a dangerous type of delirium tremens with convulsions. Major psychotic episodes with hallucinations and delusions developed only in two cases.

Table 1 shows the pharmacological composition of drugs which were most often abused. Table 2 represents the mean pain threshold and tolerance in 15 healthy volunteers. The standard deviations show that there is no interindividual uniformity of experimental pain parameters.

The mean pain threshold and tolerance in two groups (A + B) of pain patients dependent on non-narcotic analgesic combinations differed markedly from the results obtained in the healthy volunteers (Tables 2 and 3). In group A the pain threshold for forehead pressure was significantly lower than in the control subjects ($P<0.001$, one-tailed t test). There was no statistically significant difference in the pain threshold of chronic pain patients dependent on analgesic combinations (group B) and patients with similar chronic pain who did not abuse analgesics (group C).

Table 1 Drug combinations with dependence liability

Substance (mg)	*C. SUPP. (n = 10)*	*D. TBL. (n = 8)*	*O. DRG. (n = 6)*	*S.-C. SUPP. (n = 6)*
Acetylsalicylic acid	—	200	—	—
Phenacetin	—	200	—	—
Propyphenazone	—	—	125	—
Aminophenazone	—	—	—	500
Hexahydro-adiphenine	—	—	—	50
Codeine	—	10	—	40
Ergotamine	2	—	—	—
Dihydroergotamine	—	—	50	—
Belladonna-alkaloids	,25	—	—	—
Caffeine	100	50	40	—
Barbiturate	100	25	50	60

Discussion

The most striking feature of our investigation is that all patients who were dependent on non-narcotic

Table 2 Normal controls

Method	*Threshold* X ± *1 s.d.*	*Tolerance* X ± *1 s.d.*
Pressure pain: forehead (kp)	2.32 0.59	3.88 1.20
Pressure pain: tibia (kp)	2.42 0.59	4.27 1.43
Muscular pain: calf (mm Hg)	154.7 42.2	248.1 68.8
Radiant heat pain (Joules)	13.28 4.53	22.10 5.25

Table 3 Patients with chronic pain and a dependence on analgesic drugs

Method	*Group*	*Threshold* X ± *1 s.d.*	*Tolerance* X ± *1 s.d.*
Pressure pain: forehead (kp)	A	1.73 0.34	2.41 0.68
	B	1.41 0.43	2.03 0.69
	C	1.65 0.50	2.59 1.04
Pressure pain: tibia (kp)	A	1.77 0.37	2.46 0.51
	B	1.69 0.53	2.40 0.90
Muscular pain: calf (mm Hg)	A	97.0 30.1	169.3 61.7
	B	80.8 29.9	149.4 56.8
Radiant heat pain (Joules)	A	7.25 3.30	12.74 3.54
	B	6.76 2.44	13.79 2.38

analgesics took combined drugs, and not a single drug alone. This result is in agreement with observations on phenacetin abuse (Heyck, 1965). However, we observed the same phenomenon in analgesic mixtures without phenacetin (Wörz *et al.*, 1975). Obviously, psychotropic agents are the common pharmacological denominator of the problem. All patients abused compounds containing one or two mild analgesics and one to three psychotropic agents, primarily a barbiturate (Table 1). Even early reports (Bernays, 1957; Fahrni, 1950) on chronic intoxication and abuse of analgesics have shown that combinations with psychotropic drugs had been mis-used rather than single analgesics. Not all but many combinations contain barbiturates. Besides the hidden dependence potential of these sedatives, the stimulating effects of caffeine must be considered (Heyck, 1965; Wörz *et al.*, 1975).

In the vicious circle of chronic pain and analgesic dependence, an important incentive for repeated drug intake is aggravation of the pain several hours or some days after drug cessation. In the long run, however, the discontinuation of analgesics is often accompanied by a substantial decrease of pain intensity or a change from persistent into intermittent pain (Wörz *et al.*, 1975; Wörz & Gerbershagen, 1978). Therefore, withdrawal of analgesic drug mixtures is effective and appropriate therapy for some patients with chronic pain.

Our observations suggest that chronic overuse of analgesic drug mixtures increases pain sensitivity and lowers experimental pain thresholds.

Similar, but less marked lowering of the pain threshold was found in patients with chronic pain but without abuse; highly sensitive individuals seem to be over-represented among patients with chronic pain. On the other hand, experimental pain thresholds may increase after drug cessation in some patients with chronic pain who abuse analgesic combinations.

All our patients with signs and symptoms of ergotism misused combined preparations containing barbiturate and caffeine; ingredients with dependence potential seem to play an important role in the development of that dependency. On the other hand, there have been numerous observations of ergotamine abuse where psychotropic agents are not taken simultaneously (Friedman, Brazil & von Storch, 1955; Hokkanen, Waltimo & Kallanranta, 1978; Peters & Horton, 1950; Rowsell, Neylan & Wilkinson, 1973). In ergotamine-induced headache, changes of experimental pain parameters may have no significance. Therefore, at least two different mechanisms are involved in the aggravation of chronic pain by overuse of drug mixtures.

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