A QUANTITATIVE STUDY OF CUTANEOUS ANALGESIA PRODUCED BY VARIOUS OPIUM ALKALOIDS

By David I. Macht, N. B. Herman, and Charles S. Levy

PHARMACOLOGICAL LABORATORY, JOHNS HOPKINS UNIVERSITY

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The pharmacological and physiological literature contains but few quantitative and scientifically accurate comparisons of the narcotic or analgesic properties of the various opium alkaloids. This is chiefly due to a lack of an adequate method for studying the subject. The observations so far recorded are of a clinical character, and the conclusions drawn, even in the cases where alkaloids of reliable purity were used, show the greatest diversity of opinion. Thus, Claude Bernard[1] regarded narcein, an inert substance according to the majority of investigators, as a powerful narcotic; again Fronmüller[2] ranked narcotin in activity as next to morphin; while Baxt[3] extolled the wonderful pain-relieving virtues of papaverin.

In the present investigations we have made use of a large Baltzer inductorium for producing quickly and conveniently finely graded pain stimuli. Having standardized our apparatus with the help of Dr. C. W. Hewlett of the Physical Laboratory of this University, we were able to express the values of these stimuli, quantitatively, in Henrys or C. G. S. units, and in this way compare the strengths of the stimuli required to produce pain under various conditions.

The first step in the investigation was to determine whether a sufficiently constant pain threshold could be established. Martin[4] and his coworkers have studied the threshold of electrocutaneous sensation with the induction current, by dipping a finger in a liquid electrode, and have found that a definite sensory threshold can be established, subject to physiological diurnal, nocturnal, and fatigue variations. Furthermore, Martin, Grace and McGuire[5] in the only pharmacological study by this method, have found a definite lowering of the sensory threshold after administration of acetphenetidin by mouth.

In our work we have made use of fine platinum electrodes, studying the effect of the induced current on individual pain points or groups of pain points in four different regions of the body. In this way our chances of error were lowered fourfold. The points most convenient for study employed by us were the skin on the back of the hand between thumb and forefinger, the tip of the nose, the tip of the tongue, and the lips.

In complete agreement with the localization of pain points on the surface of the body, as described by v. Frey,[6] and others, we have found that at any given spot of the body a definite pain sensation can be elicited by changes in mutual inductance of sufficient intensity, and that for every group of pain points a pain sensation of exactly the same quality and intensity can be elicited by exactly the same intensity of electrical stimulus. By practice we were able to distinguish changes in pain sensation produced by moving the secondary towards or away from the primary coil a distance of not more than 0.1 cm.

Through numerous observations it was established that the normal pain threshold remains surprisingly constant for many hours in succession, and, through a series of other experiments, lasting over 25 hours each, the diurnal and nocturnal variations were found to be very slight.

Having determined the normal pain threshold in any given experiment, a drug was administered by subcutaneous or intramuscular injection, and, after its absorption, repeated readings were made. In this way a rise or fall in the pain threshold, or an analgesic or hyperalgesic effect respectively, was detected and measured. The experiments were performed on Dr. Macht and two medical students, Messrs. N. B. Herman and C. S. Levy.

Being fully aware of the fact that certain subjective elements, inherent in the character of the investigation, enter into our experiments, we have taken all possible precautions to eliminate errors arising from this source, and have made numerous control experiments.

Each experiment was carried out in the same room, and under perfectly constant conditions. Readings were always taken with the subject in the same position, and the subject was never allowed to look at the apparatus, but sat either with eyes closed or fixed on some distant point. The electrodes employed were of course the same in any one experiment; the distance, between the electrodes was kept fixed; the pressure with which they were applied to the surfaces was kept constant; the direction of their application was the same; and the wetness of the surfaces stimulated was maintained the same as nearly as could be judged.

When a drug was administered, the subject was ignorant of its nature. Furthermore, as controls, normal saline and other inactive substances were often substituted in place of the drug without the subject's knowledge. It may be remarked in passing, that owing to the conflicting experiences of previous observers, we could not know the true pharmacological action of most of the alkaloids studied; thus further eliminating any subjective bias.

Action of Opium Alkaloids Individually.—By the above methods the six principal opium alkaloids, morphin, papaverin, codein, narcotin, narcein and thebain were studied. Administered in moderate therapeutic doses, it was found that in respect to their analgesic power beginning with the strongest and ending with the weakest they ranged themselves in the following order: Morphin (10 mgs.)→Papaverin (40 mgs.)→Codein (20 mgs.)→Narcotin (30 mgs.)→Narcein (10 mgs.)→Thebain (10 mgs.).

In respect to morphin in one of us an idiocyncrasy was noted. The subject (N. B. H.) was rendered hypersensitive to pain, and this effect could be measured quantitatively. This was an interesting confirma-

TABLE SHOWING THE MAXIMAL EFFECTS OF THE VARIOUS DRUGS USED FOR D. I. M.

TIME OF READING	MORPHIN SULPHATE 10 MGS.	MORPHIN SULPHATE 5 MGS.	PAPAV. SULPH. 40 MGS.	CODEIN PHOSPH. 20 MGS.	NARCOTIN HCl 20 MGS.	NARCOTIN HCl 8 MGS.	NARCEIN HCl 10 MGS.	THEBAIN HCl 10 MGS.	NARCOPHIN 20 MGS.	NARCOPHIN 10 MGS.	NARCOPHIN 5 MGS.	PANTOPON 10 MGS.
	C.G.S. units	C.G.S. units	G.G.S. units	C.G.S. units	C.G.S. units	C.G.S. units	C.G.S. units	C.G.S. units	C.G.S. units	C.G.S. units	C.G.S. units	C.G.S. units
HAND												
Before injection.....	2553	4554	2829	2208	2484	5520	6624	7038	5451	3174	3588	4899
After injection.....	4209	4554	6210	2967	3036	5106	6210	7038	17664	5106	4209	6624
TONGUE												
Before injection....	1588	1897	1173	2208	2277	3036	2760	2622	1622	1725	1656	2070
After injection.....	3174	1794	2277	3036	2553	2760	2622	2553	3626	2829	2208	3588
LIP												
Before injection....	1002	1312	639	966	1104	2070	1312	2139	829	932	897	1156
After injection.....	2208	1380	1656	1346	1588	1794	1312	2070	4345	1139	1151	1725
NOSE												
Before injection....	1156	1002	518	1588	1244	1244	1622	1794	1156	1156	1036	1622
After injection.....	2277	1070	2484	1897	1656	1104	1520	1794	3450	2070	1380	2622

tion of the existence of undoubted cases of persons, who are not relieved by morphin, but are rendered even more sensitive by it.

Action of Combination of Alkaloids.—After a study of the individual alkaloids, the action of combinations of morphin and narcotin meconates (narcophin) and other salts were studied. It was found that a given dose of narcophin has greater analgesic power than is represented by the arithmetical sum of the effect of its constituents, morphin and narcotin. Thus 5 mgs. of narcophin produces distinct analgesia, while 5 mgs. of morphin alone, or 10 mgs. of narcotin alone, produces no such effect. This observation is in complete agreement with Straub's[7] views on synergism of these two substances. A similar action was observed with a mixture of the total opium alkaloids (Pantopon).

The accompanying table illustrates the maximal effects of the various drugs used on one of us, as expressed by the quantity of stimulus in C. G. S. units required to produce the threshold sensation of pain.

Although by the above described method only cutaneous sensations could be studied, we think that our observations are of some value in the study of the very important subject of analgesia. This research has been endowed in part by a grant from the Council on Pharmacy and Chemistry of the American Medical Association; the complete data with many tables will appear in the *Journal of Pharmacology and Experimental Therapeutics*, Vol. 7, No. 5, January, 1916.

[1] Claude Bernard, *Paris, C. R. Acad. Sci.*, 59, 406 (1864).

[2] Fronmüller, *Klin. Stud. über die narcot. Arzneimittel*, Erlangen, 1869.

[3] Baxt, *Arch. Anat. Physiol.*. 1869, p. 112.

[4] Martin, Porter and Nice, *Psychological Review*, 20, 194 (1913); Grobfield and Martin, *Amer. J. Physiol.*, 31, 300 (1913); Martin, Bigelow and Wilbur, *Ibid.* 33, 415 (1914); Martin, Wittington and Putnam, *Ibid.* 34, 97 (1914).

[5] Martin Grace and McGuire, *J. Pharmacol. Exp. Therap.*, 6, 527 (1915).

[6] von Frey, *Leipzig, Abh. Ges. Wiss.*, 66, 186, 293 (1894); 67, 166 (1895), and *J. Amer. Med. Ass.*, 47, 695 (1906).

[7] Straub, *Biochem. Zs.*, 41, 419 (1912).

THE SURFACE-TENSION AT THE INTERFACE BETWEEN TWO LIQUIDS

By William D. Harkins and E. C. Humphery

KENT CHEMICAL LABORATORY, UNIVERSITY OF CHICAGO

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While working with Haber upon a theory of muscular motion it was found by Harkins that the capillary-tube method for the determination of surface-tension is very inaccurate whenever a basic solution is used. This method is also extremely sensitive to the action of dust particles and to the presence of certain impurities, since the surface involved in the measurement is very small. Of the other available methods the two best seem to be the measurement of surface waves and the determination of the weight of a falling drop. Of these two the former requires a very elaborate and expensive apparatus if the determinations are to be made with considerable accuracy, while on the other hand the drop-weight method makes use of comparatively simple apparatus and gives results which are reproducible with considerable accuracy.

The most complete treatment of the mathematical theory of the relation between the forms of drops and surface-tension is given in a book published in 1883 by Bashforth and Adams.[1] Much later than this,