IONIZATION CONSTANTS OF SOME ANALGESICS WITH NARCOTIC ACTION AND THEIR PAIN-RELIEVING ACTIVITY

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UDC 615.212.7.011.4

The ionization constants of morphine, dihydrohydroxycodeinone, pethidine, trimeperidine, methadone, levorphanol, dextromoramide, and estocin were determined by potentiometric microtitration. The drugs studied have ionization constants (pKa) of between 5.7 and 9.0. Calculations of the degree of ionization show that at physiological pH values all the analgesics tested exist in two forms – the uncharged base and the cation – in assayable quantities. A direct relationship was found between the analgesic activity and the ionization of the compounds.

Previous work has shown that the characteristic physicochemical properties of anaesthetics play an important role in their mechanism of action [3, 4]. It was decided to examine whether other types of neurotropic activity are also linked with certain physicochemical properties of the compounds.

Many therapeutic substances are known to be ionized within the range of physiological pH values. This is an interesting fact, because in all groups of substances which have been tested (cholinolytics, local anaesthetics, etc.) the behavior of the ion differs from that of the unionized molecule of the substance [5, 6, 8, 11]. It has been shown for a series of pethidine analogues that ionization is an essential condition for manifestation of the analgesic activity of the compound [7].

The object of this investigation was to study the relationship between the basicity and the pharmacological activity of narcotic analgesics belonging to different chemical groups. The analgesics chosen for study were morphine, dihydrohydroxycodeinone (DHHC), pethidine, trimeperidine, methadone, levorphanol, dextromoramide, and estocin.

TABLE 1. Ionization Constants of Narcotic Analgesics and Their Analgesic Activity (M ± m)

Analgesic	pKa (at 22°)	Analgesic activity, (ED_{50} in mg/kg)	Analgesic	pKa (at 22°)	Analgesic activity, (ED_{50} in mg/kg)
Methadone $C_{21}H_{27}NO \cdot HCl$	9,08±0,05	7,5	Trimeperidine $C_{17}H_{25}NO_2 \cdot HCl$	8,02±0,04	9
Pethidine $C_{15}H_{21}NO_2 \cdot HCl$	8,31±0,04	30	DHHC $C_{18}H_{21}NO_4 \cdot HCl$	7,81±0,03	3,2
Estocin $C_{20}H_{25}NO_3 \cdot HCl$	8,20±0,05	28	Levorphanol $C_{17}H_{23}NO \cdot C_4H_6O_6$	5,84±0,01	2,5
Morphine $C_{17}H_{19}NO_3 \cdot HCl$	8,07±0,05	17	Dextromoramide $C_{25}H_{32}N_2O_2 \cdot C_4H_6O_6$	5,70±0,02	1,25

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TABLE 2. Degree of Ionization of Analgesics (in %) at Various pH Values

Analgesic	pKa (at 22°)	Percentage of ionization at undermentioned pH									
		4,0		5,0		6,0		7,0		7,35	
		nonionized base	cation	nonionized base	cation	nonionized base	cation	nonionized base	cation	nonionized base	cation
Methadone $C_{21}H_{27}NO \cdot HCl$	9,08±0,05	0,00084	99,99916	0,02	99,98	0,08	99,92	0,83	99,17	1,73	98,27
Pethidine $C_{15}H_{21}NO_2 \cdot HCl$	8,31±0,04	0,00214	99,99796	0,03	99,97	0,20	99,80	4,67	95,33	9,88	90,12
Estocin $C_{20}H_{25}NO_3 \cdot HCl$	8,20±0,05	0,0064	99,9936	0,07	99,93	0,64	99,36	5,94	94,06	12,75	87,25
Morphine $C_{17}H_{19}NO_3 \cdot HCl$	8,07±0,05	0,0086	99,9914	0,09	99,91	0,85	99,15	7,85	92,15	16,09	83,91
Trimeperidine $C_{17}H_{25}NO_2 \cdot HCl$	8,02±0,04	0,00955	99,99045	0,10	99,90	0,95	99,05	8,72	91,28	17,62	82,38
DHHC $C_{18}H_{21}NO_4 \cdot HCl$	7,81±0,03	0,0155	99,9845	0,16	99,84	1,54	98,46	13,43	86,57	25,75	74,25
Levorphanol $C_{17}H_{23}NO \cdot C_4H_6O_6$	5,84±0,01	1,4245	98,5755	2,63	87,37	59,11	40,89	93,53	6,47	97,00	3,00
Dextromoramide $C_{25}H_{32}N_2O_2 \cdot C_4H_6O_6$	5,70±0,02	1,956	98,044	6,64	83,36	66,62	33,38	95,23	4,77	97,81	2,19

EXPERIMENTAL METHOD

The analgesic activity of the compounds was estimated by Haffner's method [9]. Ionization constants were determined by potentiometric microtitration [1]. A type LPU-01 electronic potentiometer was used to measure pH. The solution of the analgesic (0.005 M) was treated successively with the volume of a titrated solution of alkali (0.05 M NaOH) which corresponded to 25, 50, and 75% neutralization. After each addition the solution was thoroughly mixed and the pH measured. From the pH values obtained at the three different levels of neutralization the arithmetic mean was taken. The ionization constants were calculated by the equation

$$pKa = pH + \lg [HA] - \lg [A^-]. \quad [1]$$

Five experiments were carried out with each substance and the mean values of pKa and their standard errors were calculated from the results [2]. The correlation between the ionization constants of the substances and their analgesic activity was estimated by calculating the rank correlation coefficient [10].

EXPERIMENTAL RESULTS

On the basis of their pKa values (Table 1) the compounds studied can be placed in the following groups: pethidine and estocin (8.31, 8.20); morphine, trimeperidine, and DHHC (8.07, 8.02, 7.81); levorphanol and dextromoramide (5.84, 5.70). It is interesting to note that low values of pKa were found for the highly active analgesics levorphanol and dextromoramide. As Table 1 shows, the order of arrangement of the compounds based on their pKa value and their effective analgesic dose is generally the same. Methadone, with pKa = 9.08, was an exception. Comparison of the analgesic activity of the compounds with their ability to ionize revealed a coefficient of correlation of 0.762 ± 0.158. Consequently, correlation between analgesic activity and ionization of the compounds is close.

These results indicate that the pKa values of the analgesics studied, which have a wide clinical application, lie between 5.70 and 9.08. This pKa range is the reason why molecules of the analgesics exist at physiological pH values in two forms – the uncharged base and the cationic form – in assayable amounts.

This statement can be illustrated by calculating the concentration of the ionized and nonionized forms of an analgesic at different pH values. The following equation was used for the calculation:

$$\text{Degree of ionization of analgesic (in \%)} = \frac{100}{1 + \text{antilog}\,(\text{pH} - \text{pKa})}.$$

It will be clear from Table 2 that most molecules of the analgesics are in the cationic form at pH 4.0, 5.0, 6.0, 7.0, and 7.35. Meanwhile the highly active analgesics levorphanol and dextromoramide have 60-98% of their molecules in the form of the nonionized base at pH 6.0, 7.0, and 7.35.

These results suggest that both the cationic and the nonionized form of the molecule participate in the penetration of the analgesic to the receptor and in the interaction between them.

LITERATURE CITED

1. A. Albert and E. Serjeant, Ionization Constants of Acids and Bases [Russian translation], Moscow-Leningrad (1964).
2. M. L. Belen'kii, Elements of Quantitative Evaluation of the Pharmacological Effect [in Russian], Riga (1959).
3. N. T. Pryanishnikova, in: Pain and Its Control [in Russian], Sverdlovsk (1966), p. 181.
4. N. T. Pryanishnikova, Khim.-Farmats. Zh., No. 1, 35 (1970).
5. A. Albert, Pharmacol. Rev., 4, 316 (1952).
6. E. J. Ariens and A. M. Simonis, Arch. Internat. Pharmacodyn., 141, 309 (1963).
7. A. H. Beckett and J. V. Greenhill, J. Med. Pharm. Chem., 4, 423 (1961).
8. T. C. Daniels and W. D. Kumler, in: Textbook of Organic, Medicinal, and Pharmaceutical Chemistry, Philadelphia (1956), p. 3.
9. F. Haffner, Dtsch. med. Wschr., 55, 731 (1929).
10. M. G. Kendall, The Advanced Theory of Statistics, London (1955), p. 388.
11. J. C. Skou, J. Pharm. (London), 13, 204 (1961).