Effect of Physical Activity on the Absorption Rates of Procaine Penicillin G Implants

By BERTON E. BALLARD

The pellet implantation technique was used to estimate quantitatively the effect of rat body movement on solid drug absorption rate. Animals placed in a rodent activity cage and rotated at 2.81 and 3.83 r.p.m. showed significantly greater mean absorption rates per mean area for procaine penicillin G pellets than nonrotated controls.

To DATE no study has appeared in the literature which shows the possible quantitative relationship that may exist between drug pellet absorption rate and degree of animal physical activity (1). Such a study would have theoretical as well as practical significance, because the intensity of the pharmacological, toxicological, and therapeutic response to an implanted solid drug may be directly related to the magnitude of the absorption rate of the drug.

MATERIAL AND METHODS

Implants.—Commercially available procaine penicillin G was the model drug used in these studies. After it was recrystallized from water and dried in a desiccator for 48 or more hr., it was compressed at 2.81×10^3 Kg./cm.^{2} on a Carver laboratory press designed to allow use of standard tableting machine punches and dies. The mean diameter of the disks was 0.639 cm. and their mean initial weight was 66.9 mg. (range 51.8 to 86.9 mg.). The mean apparent density of the disks was 1.167 Gm./cm.^{3}. No binders, excipients, diluents, or lubricants were added.

Implantation.—Female Sprague-Dawley rats having a mean weight of 228 Gm. (range 182 to 298 Gm.) were used in these tests. Animal weight was not rigidly controlled, because it was obvious by inspection that no correlation could be found between disk absorption rate and animal weight for any given rotational velocity. The animals were anesthetized with ethyl ether, and a ventral midline incision of about 1-cm. length was made in the abdominal skin in an anatomical region that has been defined before (2). The subcutaneous connective tissue lateral to the incision was teased apart to provide sites for the implantation of 2 preweighed disks, one to either side of the midline incision. The incision was sutured closed following the implantation of the disks. After the "rest" and exercise periods, the animals were reanesthetized and the implants removed. The disks were briefly washed with distilled water and placed to air dry for 24 hr. or more on pieces of filter paper. The disks were reweighed and the mean absorption rate per mean area, $\bar{R}/\bar{A}$, was calculated by methods previously described (3), except that no correction for the proteinaceous "ghost" weight was made, because of the short implantation times used.

Activity.—After implantation of the 2 disks, the animals were allowed to recover ("rest") from effects of anesthesia in their cages for about 2 hr. They then were placed in a rodent activity cage[1] for varying periods of time, depending in part upon the rotational velocity of the cage. The cage has a circumference of 1.13 M., and was rotated at a constant angular velocity by means of a dual shaft electronic controlled mixer[2] fitted with a small pulley having an outside diameter of 2.1 cm. A piece of laboratory rubber tubing about 140 cm. long and 8 mm. in outside diameter with the ends stapled together was wound around part of the circumferences of the pulley and cage. The revolutions per minute (r.p.m.) shown in Table I were read at the end of each exercise period from a counter attached to the wheel.

Calculation.—Because periods of rest (r) and exercise (e) varied from animal to animal and from one rotational velocity to another, Eq. 1 was used to account for these variables.

$$(\bar{R}/\bar{A})_e = \frac{[(\bar{R}/\bar{A})_t \cdot T_t] - [(\bar{R}/\bar{A})_r \cdot T_r]}{T_e} \quad \text{(Eq. 1)}$$

where $(\bar{R}/\bar{A})_e$ is the mean absorption rate per mean area attributed to the exercise period in the activity cage; $(\bar{R}/\bar{A})_t$ is the mean absorption rate per mean area for the total implantation time, T_t; the term $(\bar{R}/\bar{A})_r$ is the mean absorption rate per mean area for the rest period; T_r is the total time an implanted animal was "resting" or outside the activity cage and is the sum of the times after implantation and before exercise and after exercise up to the time of implant removal; and T_e is the time that the implanted animal was "exercising" in the activity cage.

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[1] Rodent activity cage (AC-66F), Acme Animal Care Equipment, Chicago, Ill.

[2] Cole-Palmer Instrument and Equipment Co. (No. 4650), Chicago, Ill.

TABLE I.—INTENSITY OF PHYSICAL ACTIVITY AND PROCAINE PENICILLIN G ABSORPTION DATA

r.p.m.[a]	T_e[b] (hr.)	T_r[c] (hr.)	Distance Traveled, M.	$(\bar{R}/\bar{A})_e$[d] (± 95% Confidence Limits) × 10^4 Gm./hr./cm.^{2}	p[e]
0 (12)	0	6.27	...	1.93[d] (0.29)	...
1.04 (6)	3.79	3.23	267	2.18 (0.00)	$0.20 < p < 0.25$
2.05 (8)	3.19	3.15	443	1.97 (0.00)	$0.8 < p < 0.9$
2.81 (12)	2.98	3.08	567	2.34 (0.04)	$0.001 < p < 0.005$
3.83 (7)	2.00	3.26	519	2.57 (0.03)	$0.001 < p < 0.005$

[a] Weighted mean revolutions of activity cage per minute. Number of animals is in parentheses. [b] Mean time for exercise in activity case. [c] Mean time an implanted animal was "resting" or outside the activity cage. [d] Mean absorption rate per mean area attributed to the exercise period in the activity cage as calculated by Eq. 1. The value for zero r.p.m., included for comparison purposes, is actually $(\bar{R}/A)_r$. The 95% confidence limits appear in parentheses. [e] The p value from the 2-tail t test when comparing the mean absorption rate per mean area for zero r.p.m. with rates at another r.p.m. The values at 1.04 and 2.05 r.p.m. should be considered as not significant.

RESULTS AND DISCUSSION

The results of this experiment summarized in Table I showed that when the animals' activity was substantially increased over normal values there was also a significant increase in the magnitude of the mean disk absorption rate per mean area. The present findings tend to substantiate the unverified suggestion made by Kearns (4) that the absorption rate of an implanted pellet (a steroid) could be increased if the patient would massage daily the skin area over the drug.

The results also show that the degree of dispersion about the mean values of $\bar{R}/\bar{A}$ (as reflected by the 95% confidence limits) is much broader for the animals "resting" than it is for those moving at a constant velocity on the activity wheel. The broader dispersion seen in the mean values for the "resting" animals might be expected because there was a wide variation in the intensity of body movement brought on by the use of ether as the anesthetic.

Some clinicians (5, 6) have studied the correlation between physical activity and the magnitude and duration of penicillin serum levels following an intramuscular injection of procaine or benzathine penicillin G. Elevations in penicillin serum levels observed by these investigators after vigorous exercise could be explained by the results of this experiment. If human physical activity increased the dissolution rate of the depot penicillin salt crystals, then elevations in the drug serum level should logically follow, assuming that drug elimination mechanisms remained unchanged before and after exercise.

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Cholinesterase Activity and Sulfonamide Absorption in Rats

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Rats administered, orally, a combination of neostigmine methylsulfate and sulfonamide showed an increased 4-hr. blood sulfonamide level as compared to animals administered only sulfonamide. Blood cholinesterase activity, 4 hr. after treatment, was determined and compared with that of control animals.

OVER A half-century ago Barbour and Abel (1) found that physostigmine increased the rate of diffusion of acid fuchsin in frogs. Lewis (2), in 1916, reported the same to be true for trypan red in dogs. Twenty-two years later Cole and Curtis (3) showed that acetylcholine increased the permeability of the marine organism *Nitella*. In the last decade there have been reports of the potentiation of the action of morphine in cats (4), streptomycin in rats (5), and barbital in mice (6) by pretreating with cholinesterase inhibitors. Other reported changes in drug activity brought about by anticholinesterases include the potentiation of the anesthetic activity of a given dose of phenobarbital and pentothal (7) and a lengthening of the duration of the anesthesia.

The increased permeability of *Nitella* in the presence of acetylcholine and the like phenomena seen in *P. vulgarus*, *S. typhosa*, and *P. aeruginosa* with

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