

DEMONSTRATION OF LARGACTIL (CHLORPROMAZINE HYDROCHLORIDE) IN THE URINE

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It is often of importance in a psychiatric department to ascertain whether a patient has consumed the Largactil prescribed, e.g. on occasions when a patient appears only to be slightly affected by Largactil. Dubost and Pascal demonstrated that a Largactil solution mixed with equal quantities of concentrated sulphuric acid gives a marked carmine red colour which is so stable that the intensity of the colour may be measured in a spectrophotometer. In biological fluids, Largactil must first be extracted with ether and then transferred to the aqueous phase before the determination can be undertaken. By experiments on rabbits and dogs, these authors found that up to 5 per cent. of the Largactil administered is excreted in the urine in the course of 24 hours and a total of up to 8 per cent. is excreted in the course of the first few days.

A simple method of qualitative demonstration of Largactil in the urine is obtained by employing a reagent consisting of 10 ml. 27 per cent. nitric acid + 1 ml. 2.5 per cent. NaNO₂. The reaction is carried out by adding 0.5 ml. of this reagent to 5 ml. urine. If the patient has received a large or medium dose of Largactil the urine will assume a blue or blue-violet colour and with large doses this colour is so intense that the solution becomes opaque. The colour is not stable but changes in the course of a few minutes, becoming red-violet, red and later yellowish. If the patient has received only small doses, the colour of the urine becomes only red-violet or red but even quantities as small as 75 mg. daily produce a distinct red colour. Occasionally the colour may, however, disappear so rapidly that its occurrence may be doubted but in such cases the test may be repeated with double quantities of the reagent. Phenergan, which similarly to Largactil is a derivative of phenothiazine, gives the same reaction as Largactil. In the presence of urobilin, light red Largactil reaction must be regarded sceptically, since urobilin with nitric acid assumes a pale pink colour.

The morning urines of 109 patients suffering from various mental disorders were examined with the above-named reagent. Of these, 82 investigations were undertaken without the investigator having any knowledge of the patient or the therapy employed. The patients were distributed thus:

Largactil prescribed ..	56	Largactil or Phenergan demonstrated in urine	53
Phenergan prescribed ..	2	Largactil not demonstrated in urine	56
Neither drug prescribed	51		
	109		109
	109		109

The quantity of Largactil prescribed varied from 75 to 1,200 mg. daily and two of the patients received, in addition, reserpine and 5 ritalin.

Among the patients who did not receive Largactil there were two who received 75 mg. phenergan daily. Of the remainder, 9 did not receive any drugs while 22 received reserpine and two of them ritalin, in addition. Other drugs which were administered include Antabuse (5), Restenil (2), Ronicol (2), phenantoin+Luminal (2), Mysoline+Luminal (2), phenantoin+diphenhydramine chloride (1), isonazide (1), PAS (1), insulin (1), penicillin (1) and ferric tartrate (1).

In the latter group, the urine from the two patients who had received phenergan rendered a positive Largactil reaction as anticipated while all the others were negative.

Out of the 56 for whom Largactil had been prescribed, positive Largactil reactions in the urine were obtained in only 51. There were thus 5 patients for whom Largactil had been prescribed but despite this no Largactil was excreted in the urine. The following facts were revealed concerning these patients:

No. 1: 600 mg. Largactil daily had been prescribed for this patient. He refused either to admit or deny having consumed the tablets. In the evening a nurse observed him concealing the tablets in his pocket and when confronted by her he admitted that he had not consumed the tablets prescribed. He was discharged the following day.

No. 2: 600 mg. Largactil daily had been prescribed for this patient. As the Largactil reaction in the urine was negative, the patient was kept under observation and in the evening the tablets of Largactil for the day were found in his clothes.

No. 3: 600 mg. Largactil had been prescribed for this patient daily. Largactil tablets were found in the lavatory but it remained unknown who had put them there. The urines from all the patients in this ward who were receiving Largactil were examined and this patient was the only one whose urine did not contain Largactil. The patient admitted that he had not consumed his tablets and refused to take the drug in any form.

No. 4: 600 mg. Largactil daily had been prescribed for this patient. As the urine showed a negative Largactil reaction, 200 mg. Largactil was administered in solution. The following day the urine gave a strongly positive reaction.

No. 5: 300 mg. Largactil daily had been prescribed for this patient. As the urine gave a negative reaction, 200 mg. Largactil was administered in solution. The following day there was a strongly positive Largactil reaction in the urine.

Finally, 450 mg. Largactil daily had been prescribed for a patient but only traces were found in the urine although a marked blue reaction would have been anticipated. When Largactil was then administered in solution, the urine showed a markedly positive reaction the following day and during the subsequent days the patient himself became markedly affected by Largactil. It must, therefore, be presumed that he did not take the tablets, as a rule, but had swallowed a small quantity "by mistake".

Out of the 56 patients for whom Largactil was prescribed, there were thus 6, viz. 10.7 per cent., who had not consumed the tablets and had thus avoided Largactil treatment.

The substance determined in the urine is not Largactil as such but probably an oxidation product. A solution of pure Largactil always gives a red coloration with the reagent; nor is the blue colour due to the possible influence of substances in the urine as urine to which Largactil has been added also gives a red colour even after the elapse of 24 hours.

Further, the reaction is not due to nitric acid as such but to its content of HNO_3 , and NaNO_2 is added to the reagent to ensure an adequate content of HNO_3 . Freshly prepared 27 per cent. nitric acid produces no or practically no coloration with urine containing Largactil. When set aside, particularly under the influence of light, an increasing quantity of HNO_3 is formed and nitric acid then reacts with Largactil just as the reagent employed, but 6–8 times as much nitric acid must be employed to obtain the maximal intensity of coloration. The fact that the active factor is HNO_3 is also demonstrated by the observation that the same colour reaction is obtained if 25 per cent. sulphuric acid is substituted for nitric acid in the reagent employed. Employed alone, 25 per cent. sulphuric acid does not give any colour reaction with Largactil.

SUMMARY

A simple method of quantitative determination of Largactil in the urine is described. This reaction depends upon a specific colour reaction which takes place with nitric acid + sodium nitrite. Employing this reaction, it was revealed that approximately 10 per cent of the patients for whom Largactil was prescribed did not consume the tablets.

ADDENDUM

It may be mentioned that investigations are at present being undertaken regarding the period of excretion, viz., the period from the withdrawal of medication until the urine is free from Largactil. Preliminarily, a period of excretion varying from 4 to 12 days has been found and this variation appears not to depend solely upon the quantity of Largactil consumed.

REFERENCE

DUBOST, P., and PASCAL, S. *Ann. pharmaceut. franç.*, 1953, **11**, 615.