TESTING COMPLIANCE OF DRUG TAKING-A SIMPLE BED SIDE METHOD

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ABSTRACT

Assessment of compliance in drug taking is a problem in a crowded Outpatient Department. Using riboflavin as a urinary marker is a simple and rational method. Identifying riboflavin in the urine by fluorescence on exposure to ultraviolet (UV) rays or torch light is being used in medical practice but not extensively. In this study, the validity and reliability of these methods were assessed. The sensitivity and specificity of this test by UV method was 86% and 82% for Reader I (medical person) and 82% and 94% for Reader II (paramedical person). For Reader I, the accuracy of reading by UV lamp was the same as torch light (85%) whereas for Reader II the accuracy was better with UV lamp (87%) than with torch (79%). In reading the fluorescence by UV lamp the crude agreement between the 2 readers was 82% and chance corrected agreement was 64%. UV lamp method appears to be a reliable way of assessing compliance both by medical and paramedical persons whereas torch method appears to be more reliable when used by a medical person than by a paramedical person.

Key words: *Compliance, Riboflavin, UV lamp method.*

The major problem in chronic drug therapy whether it is the treatment of epilepsy or tuberculosis is poor compliance. Most often compliance is often verified in a busy Outpatient Department from the parental history. Pill counting is not possible as many patients do not bring the drug container because either they are so illiterate or they do not want to disclose their irregularity in drug intake.

In the management of epilepsy, compliance needs to be verified especially in situations where adjustment of drug dosage is required. History alone from an ignorant illiterate parent may not give the true position. Estimation of drug level would be more accurate but it is expensive and time consuming and is not carried out in all the hospitals in our country.

Hence, it is important to have a simple, inexpensive and less time consuming bed side test to assess compliance. If a pharmacologically inert substance, which can be readily detected in an accessible body fluid, is added to the tablet under investigation, then screening of the body fluid for the inert substance would provide a technically simple test. Riboflavin, on oral administration, is absorbed in the upper gastrointestinal tract, bound to plasma protein

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in the blood and excreted in the urine as the free vitamin. This may be detected qualitatively in the urine by its fluorescence on exposure to ultraviolet light. It does not cause adverse pharmacological effects(l-3).

To assess compliance, in this study we utilized riboflavin tablets with or without active medication and screened the urine of these patients for fluorescence under ultraviolet (UV) lamp and torch light. The study had the following objectives : *(i)* To assess the validity of this test in identifying children who have taken ribflavin; *(ii)* To find out the inter observer variation in reading the fluorescence effect; and *(iii)* To determine the minimal dose of riboflavin required to produce fluorescence in the urine sample 12 to 14 hours after ingestion.

Subjects and Methods

Two methods were used to assess the presence of fluorescence in urine.

1. UV *lamp method(4):* Fluorescence was tested by exposing the urine to ultra violet light using a "ADCO cabinet type model UV-BT long wave length lamp". Urine was placed in a wide bottomed beaker with water in a similar beaker as control. When a milky white fluorescence was observed, the test was said to be positive, otherwise it was considered negative.

2. Another documented method is examining urine, in a universal blood tube, for fluorescence by a narrow beam of light emanating from a pen torch against a matt black background (5). Though this is a coarse method, its advantage is that only specimens showing high levels of riboflavin will be positive.

Forty four (44) children in the age group 4-12 years were recruited and randomized into two groups. One group was advised to take riboflavin tablet at 9 PM and to attend hospital at 9 AM the next day. The other group was advised not to take any tablet and to attend the hospital the next day. Five children belonging to the second group did not attend the hospital the next day. The volunteers were children attending seizure clinic and their siblings. No dietary restriction was imposed on the children but they were asked to avoid all medication from 24 hours prior to taking the riboflavin tablet till the completion of the test. Those on anti epileptic drugs were advised to continue the drugs. The urine samples from children who consumed riboflavin and from those who did not consume riboflavin were numbered and arranged in a random sequence by a third investigator. The coding of the sequence was kept in a file. A medical and a paramedical person were then asked to screen the urine by both methods, independently and give their results. They were totally blind to the knowledge of riboflavin consumption by children. Their results were tabulated.

In order to find out the minimal dosage of riboflavin required to produce fluorescence in urine, we recruited 75 children separately in the age group 4-12 years. These also included patients attending the seizure clinic and their siblings. These children were divided into 3 groups of 25 children each. The first group was instructed to take 10 mg of riboflavin at 9PM, the second group to take 20 mg of riboflavin at 9 PM and

the third group to take 30mg of riboflavin at 9 PM. They were all asked to report at 9 AM the next day. Samples of urine were collected at 9 AM, 10 AM and 11 AM for all 75 children. All the samples were tested for fluorescence by a medical officer using UV lamp method.

Results

Data from 39 volunteers were used for calculating test characteristics like sensitivity, specificity, positive predictive value and negative predictive value for both UV method and torch method. Inter-observer variation was calculated by kappa statistics. Data from 75 different volunteers were used to calculate the proportion of patients whose urine was positive for fluorescence test, at variable intervals after ingestion of riboflavin. Proportion of patients who had positive tests in three groups consuming 10 mg, 20 mg and 30 mg, respectively were calculated.

When UV lamp method was used, sensitivity of the test was 86% for Reader I (medical officer) and 82% for Reader II (paramedial person). The specificity of this test was 82%'and 94% and the positive predictive values were 86% and 95% for Readers I and II, respectively. When torch method was used, sensitivity of the test was 86% for Reader I and 68% for Reader II. The specificity of this test was 82% and 94% and the positive predictive values were 86% and 94% for Readers I and II, respectively. For Reader I, accuracy of reading by UV lamp was the same as torch light (85%), whereas for Reader II, the accuracy was better with UV lamp (87%) than with torch (79%).

The presence of riboflavin in the urine was identified by Reader I, by both methods, in 18 out of 22 patients given riboflavin. Reader II identified riboflavin by both methods in 15 samples. The absence of fluorescence in the urine was identified by Reader I, by both methods, in 13 out of 17 patients who were not given riboflavin. Reader II identified absence of fluorescence in the urine, by both methods in 15 out of 17 samples *(Table I).*

When test results of UV lamp method were compared between Readers I and II, 32 observations agreed out of 39. The crude agreement was 82% *(Table II)* and chance corrected agreement (Kappa) was 64%. When test results of torch method were compared between Readers I and II, 33 observations agreed out of 39. The crude agreement was 85% *(Table III)* and chance corrected agreement (Kappa) was 70%.

All 75 patients showed fluorescence upto 13 hours after consumption of riboflavin. For those who received 30 mg, 88% showed positive test even at 14 hours whereas among children who received 20 mg, only 52% showed positive test at the end of 14 hours. Of children who received 10 mg, only 32% showed fluorescence at the end of 14 hours.

Discussion

Assessment of compliance using riboflavin as a urinary marker is a technically simple and rational method. It is quick, non-invasive and can be carried out for any drug. This test could be done either in the Out Patient Department or at the bedside, both by a medical and by a non medical person(4-6).

In our study, the accuracy of UV

TABLE I—*Identification of Fluorescence by UV Method and Torch Method*

Riboflavin taken	Reader	No. of children in whom fluorescence was observed by			
		Both UV & torch	UV only	Torch only	Neither torch nor UV
Yes (n=22)	I	18	1	0	3
	II	15	3	0	4
		No. of children in whom fluorescence was not observed by			
		Both UV & torch	UV only	Torch only	Neither torch nor UV
No (n=17)	I	13	0	1	3
	II	15	1	1	0

TABLE II—*Inter Observer Variation—UV Method*

Reader II	Reader I		
	Positive	Negative	Total
Positive	17	2	19
Negative	5	15	20
Total	22	17	39

TABLE III—*Inter Observer Variation—Torch Method*

Reader II	Reader I		
	Positive	Negative	Total
Positive	16	0	16
Negative	6	17	23
Total	22	17	39

lamp method for the two readers was 85% and 87% and for torch method it was 85% and 79%, respectively. The inter-observer agreement as assessed by Kappa statistic was moderate. The study by Jones also revealed the accuracy of torch method to be 92%(5).

In the group that ingested 30 mg of riboflavin, a high proportion (88%) showed positive urine results at 14 hours whereas in the group that received 10 mg, a very low proportion (32%) showed fluorescence at the end of 14 hours. The higher the amount of riboflavin ingested, the greater is the proportion detected as riboflavin positive. Similarly riboflavin can be detected in the urine for a longer period when more is ingested. A minimal dose of 10 mg is adequate to detect riboflavin in the urine upto 13 hours in all patients.

Similar observations have been made by other authors(7).

A limitation to this technique is that occasional false positive and false negative results can occur. False positive readings could occur due to increased ingestion of foods containing riboflavin. False negative readings could be due to fast urinary excretion of the vitamin. The presence of phosphates and cells in the urine can impair its translucency and make reading difficult. Addition of acetic acid clears phosphates and cells usually settle down if left for half an hour(5).

It is possible for the patient who consciously sets out to mislead the clinician and who knows about the method, to succeed by taking a tablet or two before he is seen, but this is not likely to be a common phenomenon. Probably, factors at a much less conscious level are responsible for irregular medication, and perhaps this method will allow some of these factors to be investigated(5).

In conclusion, we recommend that UV lamp method be adapted to assess compliance of drug intake in any situation where long term therapy is required. Torch method appears to be less accurate then UV method.

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