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ROLE OF QUANTITATIVE AND DYNAMIC RADIOACTIVE STUDIES IN RENAL TESTING

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INTRODUCTION

Renal radioactive tests, which play an important role in Nuclear Medicine, are currently used throughout the world (1-3). Of these tests, renograms and scintigrams are the most widely used. Such success is, in fact, more apparent than real. If we consider not the frequency of use but rather the effective utility of the information provided, we are suprised to observe the lack of usefulness of these tests to urologists and nephrologists.

The lack of interest in scintigrams is not surprising, especially at present when static images compete with those obtained by radiographic, sonographic and axial tomographic methods, spatial resolution of which is an order of magnitude better. That there is a lack of usefulness, in renal dynamic and quantitative tests is much more surprising. The future of Nuclear Medicine is often considered in terms of such tests, especially since important technical improvements covering the acquisition and processing of data have been developed in the last years. Why is the original contribution of such methods so unimportant ?

The answer can only be given by users, i.e. nephrologists and urologists who complain that these tests do not correspond to their needs. A better understanding of such needs could aid in developing better adapted tests. We shall first consider dynamic and quantitative tests now available and determine why there is such a lack of interest in them. Next we shall look at the real needs of nephrologists and urologists, and finally we shall study the direction in which research should be oriented in order to satisfy their needs.

RESUME

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"Rôle des études quantitatives et dynamiques pour l'étude de la fonction rénale."

De nombreux tests radioactifs dynamiques et quantitatifs sont utilisés actuellement pour l'étude de la fonction rénale. Qu'il s'agisse de tests dynamiques morphologiques comme les images séquentielles, des tests dynamiques quantitatifs comme le rénogramme ou de tests statiques quantitatifs comme les clearances radioactives, leur apport réel et original est médiocre. Un seul apporte une information originale : le test de fixation rénale du Hg; il est d'habitude écarté en raison de la dose de radiation absorbée par le rein chez l'enfant.

L'examen des causes de ce défaut d'efficacité amène à constater que ces examens sont mal adaptés à la demande des spécialistes du rein. Ils sont basés,pour la plupart, sur le remplacement d'un indicateur "froid" par un indicateur radioactif et les avantages escomptés par l'utilisation de radioéléments ne sont pas évidents, ils sont, en effet, souvent annulés par les défauts de la détection externe.

Pour l'avenir, il paraît indispensable d'abandonner certaines conceptions traditionnelles qui nous poussent à considérer que la seule fonction rénale exploitable est représentée par l'excrétion. Le rein possède d'autres fonctions : l'une des plus intéressantes paraît être la fonction de fixation des métaux lourds et des substances toxiques dont l'étude n'est possible qu'avec l'aide des radioéléments. On peut logiquement espérer qu'une nouvelle génération de tests radioactifs, basés sur l'étude de la fixation et aussi sur l'étude d'autres fonctions rénales, pourrait apporter les informations dynamiques ou quantitatives dont le praticien a un besoin urgent.

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DYNAMIC AND QUANTITATIVE TESTS NOW USED

A. Dynamic tests. By this term we designate the kinetics of images or sequence of images still called sequential images which are in fact dynamic morphological tests, and kinetics presented in the form of curves which are dynamic quantitative tests.

1) Dynamic morphological tests are carried out using various substances which can be broken down into two groups depending on whether they are temporarely intravascular or excreted by the kidney (4-7).

^{99m}Tc pertechnetate was the best known of the intravascular agents used in renal testing. Images are obtained of the large vessels, mainly aorta , and renal perfusion.

^{131}I - OIH, ^{99m}Tc DTPA and ^{99m}Tc DMSA are the best known of the indicators excreted by the kidney. The images obtained are much more varied, the earliest 0 to 45 seconds provide data on the large vessels and renal vascularization as with pertechnetate; such is the case especially with DTPA. The following images, especially from 2 to 5 minutes, represent the renal functional parenchyma; later images provide data on the excretory tract.

The images of the large vessels and renal perfusion cannot rival those obtained by aortography but their interest lies in their use of a non-traumatizing technique. The latter may aid physicians indetermining whether to use an aortography or not.

The images of the renal parenchyma demonstrate function whereas the I.V.P. better demonstrates the calices and pelvis.

Images of the excretory tract are of little interest compared with those obtained by urography. Their only advantage is that they involve irradiation of the ovaries which is approximately 10 times less. If we seek only 'original' information, i.e. that not available from other tests and useful and also those obtained with less inconvenience for patients, only two advantages are obtained visualization of the aorta and visualization of the functional parenchyma. The original contribution of these tests is consequently slight.

2) Dynamic quantitative tests. The renogram is the best example of such tests as well as the oldest since it was described by TAPLIN 22 years ago. Carried out with ^{131}I-OIH, it aroused much expectation and engendered a great deal of research and publication in all

countries. At present, it is considered to provide almost no original information . Three other indications, accepted for a long time, diagnosis of stenosis of the renal artery , identification of obstructive uropathies and study of tranplanted kidney problems are no longer retained, the first because it is unreliable , the second because it does not add anything to a good intravenous urography, the third because it is replaced by sequential scintiphotos.

These failures were often attributed to poor standardization of the test as well as to poor interpretation of the curves. Time has shown that efforts made to improve standardization and mathematical study of the curves have not improved the quality of information provided by this test (1-3, 8,9).

Another kinetic test was codified by ROSENTHALL with ^{99m}Tc-pertechnetate and then with ^{99m}Tc glucoheptonate (7). Transit time can be calculated for the aorta and the two kidneys by recording on video tape or by a more elaborate data processing system. A small difference between the transit time for both kidneys and a large difference between the transit time for one kidney and that for the aorta would indicate stenosis of the renal artery . In fact, such abnormalities do not seem to be specific to renovascular hypertension.

^{99m}Tc DTPA was recently proposed in order to carry out quantitative kinetic studies. Such research is too recent to be included in this paper .

Almost no original information is derive from such quantitative kinetic studies.

B - Quantitative Static Tests . We include under this term tests which directly obtain the absolute value of a physiological process or function such as radioactive clearances and the Hg uptake test. These two tests study a function or a series of functions and quantifies them, in ml/min for radioactive clearances and in % of the normal for Hg uptake.

1) Radioactive clearances. These can be carried out with inulin-like substances or PAH-like substances. The technique described are numercus, with or without collection of urine or blood and with or without continous infusion (10). Theoretically they have a reputation of being simpler than conventional inulin, creatinine and PAH clearances because it is easy to measure the radioactive indicator. This is true for ^{131}I-O

clearance which is much simpler than PAH clearance. However, clearances carried out with inulin-like substances are no longer simple and perhaps no more accurate than creatinine clearance.

The original contribution is consequently limited to the convenience of labelled -OIH- clearance.

Much research has been done on measuring ^{131}I Hippuran in each kidney, using the renogram curve. If with TAPLIN, we admit that the ratio of the slope of the second segment equals the ratio of the blood flows of each kidney,[13] we can easily calculate the clearance of each kidney from the value of the total clearance of Hippuran. Several calculating techniques have been described. Some use only the initial part of the second segment; others use the surface covered by this initial part of the second segment. This hypothesis can be accepted for a normal patient. If the urinary tract is obstructed and urine accumulates in the renal cavities, this is still no proof that the basic hypothesis is valid. Despite their interest, we can place such clearances among semi-quantitative tests. In fact, they do not directly provide the absolute value of the clearance of each , the value of the slope or surface is experimentally measured but the individual clearances are obtained by using the total clearance of Hippuran which is calculated separately.

The avoid the cause of error represented by the accumulation of urine in the renal cavities, we may select the external, essentially cortical, region of the kidney on the image obtained with a computer(4). This method has, however, the disadvantage of overlooking an unknown amount of healthy parenchyma as well as the renal cavities, by avoiding one cause for error, it adds another.

2) Hg renal uptake. Many toxic substances are fixed,i.e 'permanently' sequestrated by the kidneys. Such uptake generally remains stable for a relatively long time. With $^{197}HgCl_2$, the uptake rate reaches a plateau as of the 24th hour following injection. It has been shown that the uptake rate is a faithful renal functional index. Expressed in % of the normal value for each kidney, it quantifies the function of each kidney accurately(14) . Despite its practical interest, it is little used because of the radiation dose absorbed by the kidney. The latter is approximately 5 rads in an adult and older children and 8 to 9 rads in children under 10.

Data provided by this test is original. It is,however, little used because of the radiation dose received .

If we consider not the totality of data which such tests can provide but rather their original contribution, the balance sheet is rather mediocre. It easily explains the skepticism of our colleagues, nephrologists and urologists. This practical aspect of the problem must be clearly differentiated from the frequency of utilization. One test, such as the renogram, is still often used although its best advocates have stressed the limitation of its indications. Another test, such as Hg uptake, is only exceptionally used although the usefulness of the data which it provides is progressively recognized. Moreover, considered individually, one or another urologist may be satisfied with the contribution of one or another of these tests in a narrow field. Nonetheless, it is true that their role in studying renal function and morphology is extremely limited.

WHY DO DYNAMIC OR QUANTITATIVE RADIOACTIVE TESTS HAVE SUCH A SMALL ROLE IN RENAL STUDIES ?

To answer this question, we must examine the effective needs of nephrologists and urologists. Both need tests allowing them to detect a renal lesion as early as possible and to follow its evolution with a maximum of accuracy. This can be obtained by stuying renal morphology or (and) function. Why the radioactive tests now used, morphological for some and quantitative for others, not provide the data needed?

If we examine morphological tests closely, we can see that none satisfies the needs listed above. The poor definition of our images will not allow us to make an early diagnosis, especially with tests in which a lesion is pinpointed by a hypoactive zone. In order to detect small lesions we would need excellent definition or (and) substances with an affinity for pathological tissue, i.e. allowing us to obtain positive images.

If we are to satisfy with quantitative dynamic tests the needs examined , we must accurately know the normal kinetics of the substance studied and the normal values must have a confidence interval as low as possible. In the case of Hippuran , parameters described are numerous and have not survived efforts at standardization; and their standard deviation is not accepted despite efforts made for more than 15 years. For the test proposed by Rosenthall, we still do not have either several years after its description.

Quantitative static tests only meet the needs indicated if their normal values are defined and if the confidence interval is narrow. For radioactive clearances, none has been the subject of an exhaustive work, probably because of the many methods described; and we still do not have any normal values and standard deviation. The latter are only known for conventional non radioactive inulin and PAH clearances, the relative standard deviation of which is approximately 25% (15). For measuring Hg renal uptake, the normal values are well known and the relative standard deviation of 13% is acceptable.

Along with specific needs of nephrologists and urologists, we must take into account general rules which a diagnostic test must satisfy. It must not present any danger whether involving the toxicity of the substance injected or the radiation dose delivered. For all the tests studied, the absence of toxicity is recognised, however, because of the radiation dose absorbed by the kidneys, the Hg renal uptake test is often judged unacceptable. The annual maximum acceptable dose of 3 rads for a diagnostic test with children is in fact considerably exceeded in children under 10.

This rapid survey indicates why tests now used are poorly adapted to the needs of kidney specialists.

THE FUTURE OF DYNAMIC AND QUANTITATIVE RENAL TESTS

It is difficult to imagine that radioelements with the advantages of external detection do not have an effective application in nephrology and urology. We perhaps need to open new paths and stimulate research in directions until now neglected in order to succeed in this. At the present time, all tests on the kidney with radioactive or non-radioactive substances except arteriography and Hg renal uptake study the function of excretion. All measure a kinetics of excretion or a power of excretion. Excretion is certainly an essential function of the kidney but it is not the only function. Moreover, the kidney is a profound organ surrounded by vascularized tissue and the methods of studying the excretion of a radioactive substance, by external counting, are handicapped compared with methods for measuring the clearance of a non-radioactive substance. In fact, the most interesting measurements are made in the 20 or 30 minutes following the rapid injection of the radioactive indicator; the renal concentration of the substance studied is high during this initial period but the blood concentration of this same substance is also high so that

the correction for extrarenal blood radioactivity is always high. Consequently this correction is approximate (19). Under such conditions we can easily predict that the accuracy of the final result will be low. A second weakness in the methods used for renal excretion of a substance by external counting is valid only for patients having obstructive uropathies. In obstructive uropathy urine accumulates in the renal cavities and such cumulative urinary activity is mistaken for renal activity. Methods using cortical zones of interest provide only partial aid, as have seen above. A final criticism may be made of clearance tests. We have had available for 20 years, due to the meticulous research of Homer SMITH , inulin and PAH clearance tests, for which we know the exact normal values and standard deviation. A posteriori we are led to wonder whether their contribution has not been disappointing in renal pathology. Their usefulness in physiology is well known but in renal pathology it is not obvious. Is this relative failure due to their relative inaccuracy (their standard deviation is approximately 25%) or to the fact that they provide data on glomerular or glomerulo-tubular flows , and not on an active cellular function such as the Tm of PAH or the Tm of glucose? Doubt momentarily exists.

A maximum effort should be made to engender new tests based on renal functions other than the function of excretion; among the former : are;complex metabolic functions : uptake function of toxic substances and heavy metals, : hormonal function (16). Of these, the uptake function is easier to study. The term "uptake" here designates a more or less definitive fixation not or negligibly accompanied by urinary excretion (17). It is observed with heavy metals (Hg,Tl, Au, U,Bi) and may be with other metals. Some organic poisons and various substances known for their renal toxicity also apparently have a renal fixation. Tl has an interesting medullary uptake but its pratical use is rendered difficult by uptake and massive gut excretion (18). Bi has an uptake rate almost as high as Hg but it also has a high urinary excretion which hinders measuring effective uptake rate or necessitates delaying measurement until the second or third day after injection (19). The renal uptake of Pt and W might be more interesting. With ^{99}Tc DMSA renal uptake is observed but is accompanied by significant urinary excretion during the first period of 24 hours (14), and above all its uptake rate varies from one sample to another, making it unsuitable for an exact quantitative study(19). It has apparently been established that it presents two fractions, one excreted and the other fixed; and the conditions under which the respective propor-

tions of these two fractions can no longer vary are not well known(20). ^{99m}Tc gluconate also has an uptake and a high excreted fraction (21), which is probably also true of ^{99m}Tc penicillamine. It is perhaps not improbable that we can separate in these latter substances the fraction excreted from the fraction fixed and that we can only inject the second.

The metabolic function of the kidney would be interesting to study especially at present when we are beginning to use ^{11}C and ^{13}N due to small medical cyclotrons. A lot of molecules are conjugated in the kidney and research on their renal kinetics could provide interesting data.

CONCLUSION

Most of our dynamic and quantitative radioactive tests on the kidney imitate conventional non-radioactive tests, and they contribute little new to the study of renal function. We hope that in the next years they will be developed in original directions as, for example, studies of renal uptake. Such tests better adapted to the constraints imposed by radioelements have the advantage of being quantitative and could provide much new data of use to kidney specialists.

SUMMARY

Many dynamic and quantitative radioactive tests are at present used in studying renal function. Whether involving dynamic morphological tests such as sequential images, dynamic quantitative tests such as the renogram or quantitative static tests such as radioactive clearances, their effective and original contribution is rather unimportant .Only one provides original data, the Hg renal uptake test but it is generally avoided due to the radiation dose absorbed by the kidney in children.

A study of the causes of this lack of effectiveness leads to the observation that such tests are not well adapted to the needs of kidneys specialists. They are for the most part based on replacing a "cold" indicator by radioactive indicator and the advantages anticipated from using radionuclide are not evident. In fact, they are often cancelled by the shortcomings of external detection.

For the future, it seems indispensable to abandon some traditional concepts which lead us to consider that the only exploitable renal function is represented by excretion. The kidney has other functions; one of the most interesting seems to be the function of uptake of heavy metals and toxic substances,a study of which is only possible

using radionuclides. We can logically hope that a new generation of radioactive tests based on a study of uptake and also on a study of other renal functions may provide dynamic or quantitative data which physician urgently need.

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