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BİLİMSEL TARAMALAR / SCIENTIFIC REVIEWS

Technethium 99m-DTPA

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Summary : *Tc-99m-DTPA is a widely used agent in nuclear medicine practice. For more than two decades it has been subjected to many experimental and clinical studies. This molecule, because of its suitable characteristics can also be used in labeling new drug carrier systems.*

This review tries to summarize the chemistry, preparation, dosage, pharmacokinetics, precautions, quality control, radiation dose and clinical and experimental applications of Tc-99m-DTPA.

Keywords *: Tc-99m-DTPA, Formulation, Quality control, In Vitro and In Vivo Usage*

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Teknesyum 99m-DTPA

Özet : *Tc-99m-DTPA nükleer tıpta sık kullanılan bir ajandır. Son 20 yıl içinde klinik ve deneysel bir çok çalışmayla araştırılmıştır. Bu molekül özellikleri gereği yeni ilaç taşıyıcı sistemleri işaretlemede de kullanılabilir.*

Bu derlemede Tc-99m-DTPA'nın kimyası, hazırlanması, çeşitli amaçlar için önerilen dozu, farmakokinetiği, uygulama sırasında alınması gerekli önlemler, kalite kontrolü, radyasyon dozu, klinik ve deneysel kullanım alanları ile bilgiler özetlenmeye çalışılmıştır.

Anahtar kelimeler *: Tc-99m-DTPA, Formülasyon, Kalite kontrolü, in vitro ve in vivo Kullanım*

Introduction

The chelating agent DTPA labeled with Tc-99m is mainly useful for brain, renal and blood flow imaging studies[1]. This widely used imaging agent, Tc-99m-DTPA, was first introduced to clinical nuclear medicine in 1967 by Richards and Atkins[2]. Following decades showed great progress in this field. In this paper some basic aspects of the chemistry and clinical utility of Tc-99m-DTPA are summarized.

Chemistry

Tc-99m pentetate (DTPA or Diethylene Triamine Penta Acetic acid) is sodium [N,N-bis[2-bis carbamoxymethyl amino]-ethyl]-glycinato (5-)-tecnetate(1-)-Tc-99m[3].The chemical structure of pentetate is shown in Figure 1.

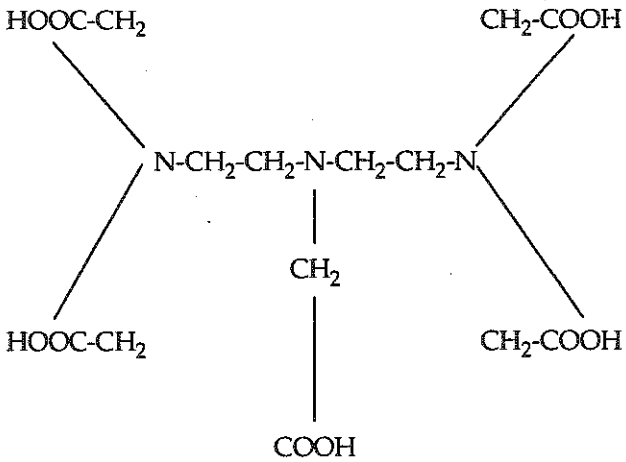

Figure 1. Chemical Structure of Pentetate (DTPA)

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Preparation

Four methods of DTPA chelate preparation have been described. Comparison of the biological behavior of these compounds containing DTPA and Tc-99m showed that only Tc-99m-DTPA and Tc-99m-DTPA(Sn) are true chelates. The third compound which is named as Renotec and contains ascorbic acid and ferric chloride is similar to Tc-99m-Fe-ascorbic acid in behavior. The fourth compound is prepared by titanous ion but is less convenient. Also considerable manipulation is necessary for the preparation of Tc-99m-DTPA (Fe) compound, because of uncomplexed pertechnetate. On the other hand Tc-99m-DTPA preparation is far more convenient and less time consuming[4,5].

The products of these labeling methods have not been conclusively identified. One of the byproducts routinely obtained by labeling with stannous ion appears to be a single radiochemically pure species, since a variety of radioanalytic separations all yield a single fraction. It has a double negative charge. Under some conditions that have not been well defined, Tc-99m-DTPA is rapidly oxidized to pertechnetate by atmospheric oxygen.Such oxidation occurs to a greater or lesser extent with virtually all technetium pharmaceuticals but is less troublesome with Tc-99m-DTPA than with most[6].

With using the commercial kit, Tc-99m-DTPA is prepared simply by adding 99m-TcO_4- to the vial and mixing it for about one minute. The labeling efficiency is greater than 95 percent. After preparation, Tc-99m-DTPA is stable for almost six hours. The oxidation state of technetium in Tc-99m-DTPA has been postulated to be 3(+) from the evidence of analytical studies[1]. Formulation data for some currently available Tc-99m-DTPA kits are shown in Table I.

Dosage and Pharmacokinetics

The suggested dose range for renal imaging studies with intravenously administered Tc-99m-DTPA in the average adult patient (70 kg) is 10-15 mCi. Administered doses for pediatric patients are individualized as a proportion of the adult dose based either on body weight or body surface area. For a conventional brain scan 10-20 mCi of Tc-99m-DTPA is used, for radionuclide sisternography a

Table I. Formulation Data For Some Currently Available Tc-99m-DTPA Kits

Trade Name	Manufacturer	Formulation
AN-DTPA	CIS-US	20.6 mg Ca_3Na-DTPA 0.15-0.3 mg $Sncl_2.2H_2O$ pH: 3.9-4.1
MPI-DTPA	MediPhysics	5.0 mg Sodium-DTPA 0.25 mg $SnCl_2$ pH:4.0-7.5
Techne Plex	Squibb	10.0 mg Ca_3Na-DTPA 0.50 mg $SnCl_2$
Tc-DTPA	Soreq	5.0 mg Ca_3Na-DTPA 0.25 mg $SnCl_2$ anhydrous
Amerscan-Pentetate	Amersham	20.6 mg Ca_3Na-DTPA 0.25 mg $SnCl_2.2H_2O$ 2.0 mg Na-p-aminobenzoate
Technescan-DTPA	Mallinckrodt	25.0 mg Ca_3Na-DTPA $SnCl_2$ and Gentisic acid
Solco-DTPA	Solco	6.0 mg Ca_3Na-DTPA 0.9 mg $SnCl_2.2H_2O$

dose of 2-7 mCi is preferred. While blood flow imaging requires 15-20 mCi of Tc-99m-DTPA, other local studies require considerably lower doses[3,7].

Following intravenous injection Tc-99m-DTPA is rapidly distributed throughout the extracellular fluid compartment.However about two hours are required to penetrate to the extracellular fluid compartment and in the presence of edema, even a longer time is necessary. Tc-99m-DTPA does not enter the cell cytoplasm. This is both due to its lipid insolubility and its net electronegative charge which makes plasma membrane impermeable to this molecule. Plasma clearance is multiexponential with biological half-lives of 3.8 minutes (58%), 16 minutes (24%), two hours (16%), and 14 hours (2%). The extremely fast component represents diffusion into the extravascular extracellular fluid space, whereas the slowest component probably represents plasma protein binding. It is rapidly and completely eliminated from the body by glomerular filtration with only trace amounts found in the bile[8].

The fraction of the administered dose remaining in the plasma is approximately 15-20 percent after one

hour, 10-12 percent after two hours and 4 percent after six hours. Plasma clearance may be delayed in patients with renal disease[9]. Whole body clearance is biexponential with biological half-lives of 1.0 hour (58%) and 9.2 hours (42%), resulting in an overall effective half-live of about 2.2 hours. Approximately 50% of the injected dose is eliminated in the urine in the first two hours and about 95% at 24 hours[10].

Precautions

When Tc-99m-DTPA is employed for measuring renal function, quality control analyses is advisable to ensure the amounts of radiochemical impurities or radiolabeled byproducts are minimal. Unfortunately no simple quality assurance technique is available for the routine determination of anticipated protein binding in vivo. The presence of unidentified impurities that bind to plasma proteins reduces the clearance rate of radioactivity from blood[11].

Another consideration in quality control is that the amount of free, unbound Tc-99m pertechnetate should be kept as low as possible. Significant levels of free pertecnetate may arise either from incomplete reduction or complexation of technetium to DTPA during the labeling process or from subsequent decomposition and oxidation of reduced technetium back to free pertechnetate. Factors associated with low labeling efficiencies include the presence of oxidants, large amounts of competing radiometals such as carrier Tc-99m and high amounts of Tc-99m pertechnetate activity during on site kit preparation. Other causes of significant degradation include prolonged time after preparation, large amounts of radioactivity in the vial and excessive dilution of the product[12].

In renal function studies, patients should be adequately hydrated, otherwise decreased urine flow may result in poor renal images.

Tc-99m-DTPA can cross the placenta, therefore it should be given during pregnancy only if clearly indicated and if benefits outweigh any potential risk [13]. A small fraction of the administered activity is excreted in breast milk. Withholding breast feeding for four hours is adequate.

As adverse reactions, the widespread use of Tc-99m-DTPA, mostly for renal studies, has brought a small incidence of vasomotor problems. Signs and symptoms of falling blood pressures predominate, resulting in loss of consciousness quite often. Evidence of an immunological process such as skin reactions or bronchospasm, is mostly unusual but a few cases have been reported following inhalation of Tc-99m-DTPA aerosol. Intrathecal route is particularly sensitive to contaminants, overdose and apparent misformulations. This form is capable of gross chelation with cerebrospinal fluid calcium and magnesium, causing gradual onset of severe neurological signs and several cases of permanent saddle anesthesia and loss of sphincter control. One has to be more alert during intrathecal and inhalation use[14,15]

Quality Control

A variety of methods are available for the analytic quality control of Tc-99m-DTPA. A kit for Tc-99m-DTPA can be assured for sterility, apyrogenicity and nontoxicity but there remains uncertainities about radiochemical purity and in vivo - in vitro protein binding[6,17]. The reported radiochemical purities of the different preparations vary from no detectable free pertechnetate to 20% pertechnetate six hours after the preparation. The radiochemical purity varies not only between different preparations but even from batch to batch, with the age of the kit and of preparation and storage temperature. The radiochemical purity is also affected by the choice and age of Mo-99 -Tc-99m generator , the amount of the activity added to the kit and the number of withdrawn doses. The radiochemical purity can be tested by gel filtration chromatography, electrophoresis, ion exchange chromatography or partition chromatography[3,6,16]. The compendial requirements (U.S.P.XXI) for Tc-99m-DTPA and techniques for determination of radiochemical purity is shown in Table II.

Quality control is a major problem with Tc-99m-DTPA preparation that is intended for measurement of glomerular filtration rate (GFR). Significant differences have been noted between the products of different manufacturers, probably due to the presence of impurities that bind to the plasma proteins. Unfortunately no method of chemical analysis has yet been shown to predict the extent of protein binding in patients. Hosain has suggested using a dual tracer technique in dogs to compare Tc-99m-DTPA

Table II. Compendial Requirements (U.S.P. XXI) and Radiochemical Analysis Techniques

COMPENDIAL REQUIREMENTS	
TC-99-M-DTPA	
pH	3.8-7.5
Radiochemical purity	> 90%
RADIOCHEMICAL ANALYSIS TECHNIQUES	
Radiochemical Component	Free unbound pertechnetate
Mobile phase	Methyl ethyl ketone/acetone
Stationary phase	Whatman 31ET (or ITLC-SG)
Rf values	Bound chelate:0.0 Free pertechnetate:1.0 Hydrolyzed, reduced Tc99M:0.0
Radiochemical Component	Hydrolyzed-Reduced Tc-99m
Mobile phase	Saline
Stationary phase	ITLC-SG
Rf values	Bound chelate:1.0 Free pertechnetate:1.0 Hydrolyzed, reduced Tc99m:0.0

preperations with a reference GFR agent[17]. Ultrafiltration using a centrifugal micropartition system with membrane filters and gel filtration using mini columns prepacked with Sephadex or Dextran are other methods that can be used for measurement of in vivo protein binding[18,19].

The quality control of Tc-99mO4, radionuclidic purity can be determined by gamma counter on the basis of different energies of Mo-99 and Tc-99m. Chemical purity test can be performed to determine Al_2O_3 content with a colorimetric spot test using aurin tricarboxylic acid.

Radiation Dose

The critical organ after the administration of Tc-99m-DTPA is the bladder wall, which sustains a radiation absorbed dose of 0.55 rad/mCi assuming no voiding and 0.115 rad/mCi and 0.27 rad/mCi with 2.0 hour and 4.8 hour voiding periods respectively. For a given blood clearance rate, the radiation dose to the bladder wall will be dependent on the urine content of the bladder at the time of injection, the urine flow rate, and the residence time in the bladder. Adequate hydration and frequent voiding are thus recommended[20,21]. Radiation dose estimates in adults for Tc-99m-DTPA is shown in Table III.

Table III. Radiation Dose Estimates for Tc-99m-DTPA

RADIATION DOSE ESTIMATES OF TC-99M-DTPA[21]	
Organ or tissue	Radiation Dose (rad/mCi)
Bladder wall	0.28
Kidneys	0.022
Liver	—
Ovaries	0.019
Bone marrow	0.012
Testes	0.013
Total Body	0.0091

Other Applications

Technetium-99m-DTPA can be used in aerosol form for pulmonary ventilation studies. Main concern is the measure of particle size because it affects the efficiency of delivery and clearance characteristics[22]. A new delivery system-aerosol production equipment (APE) which generates a particulate aerosol of Tc-99m-DTPA with a mass-median aerodynamic diameter of 0.35mm has been generated to overcome this problem[23]. Tc-99m-DTPA pellet formulations have been used to study gastrointestinal transit in humans and it showed to be an effective agent for the motility studies[24]. Tc-99m-DTPA microcapsules have also been studied in many patients and found to be safe and stable[25]. Different liposome formulations, as new drug carrier systems were also labeled with Tc-99m-DTPA and their biodistributions and stabilities were studied[26-29].

Result

This review mainly focused on the basic properties and clinical utilities of Tc-99m-DTPA. This is a widely used agent in daily nuclear medicine practice like the other Tc-99m radiopharmaceuticals[30,31]. It is mainly used for renal, brain and blood flow imaging. However, there remains a wide spectrum of applications for this molecule, among which its usage for labeling new drug carrier systems should be noted.

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