

A Discussion on the Utility of Various Routes of Administration of Octreotide Acetate

By: Eugene A. Woltering MD FACS

The James D. Rives Professor of Surgery and Neurosciences
Louisiana State University Health Sciences Center
New Orleans LA 70065
504-568-2344

The drug octreotide acetate is part of a class of drugs known as somatostatin analogs (or more properly termed peptidomimetics). This class of drugs includes octreotide, lanreotide and most recently, vapreotide. All of these drugs are octapeptides (have 8 amino acids) and can be given subcutaneously, intravenously or by depot injections of a slow release form of the compound.

Octreotide LAR ([Sandostatin LAR® Novartis Pharmaceuticals, East Hanover, New Jersey](#)) is the only slow release form of this class of drugs that is currently available in the USA. This drug is created by coating small droplets of octreotide in a polyglycolic acid shell—thus creating what are called microspheres. When given as a deep intramuscular injection, the shell coating of this drug slowly dissolves and releases the octreotide acetate. When released, the octreotide is absorbed by the surrounding tissue and sent along through the blood stream. After injection of the LAR there is an immediate release of some of the octreotide that clings to the outside of the microsphere, a phenomena known as wash off. This wash off can cause transient high levels of octreotide that remain in the blood for a few hours. Thus NET patients should never have their blood drawn for marker levels immediately after an injection of LAR; rather blood drawing for marker determination should be done immediately before LAR's injection.

Following injection of the LAR product the plasma octreotide levels begin to rise and peak at 14 days after the injection. These levels begin to fall until the next injection (usually 28 days later, in most patients). By day 28 the octreotide levels are significantly lower than the peak levels—but they never go to zero. The octreotide levels after one injection (day 28) are, in turn, less than octreotide levels after the second or even third injections (days 56 and 84). Thus it takes on average three monthly LAR injections for the octreotide levels to stabilize at what is called “steady state”. However, if one needs to get off of LAR therapy, the same mathematics that control the progressive increases in blood drug levels are present—i.e. drug levels will take about three months to drop back to near zero. This is critical in patient who are about to undergo therapy with the radiolabeled forms of somatostatin analogs—in those patients it may take 3 months or longer to get rid of the circulating octreotide in the blood. In a similar fashion those patients who have had negative Octreoscans while on LAR may consider going off of LAR for 3 months or longer to obtain the maximum sensitivity for this test.

Recently, Woltering et al have completed a study of patients on LAR at various doses and have shown that for any dose of LAR the patient's weight makes a marked difference in the blood levels of drug achieved. Thus, we currently recommend that when starting LAR therapy in heavier patients that clinicians choose the 30 mg/mo dose while lighter patients may do equally well on 20 mg/month. The table below shows the mean \pm SD plasma drug levels of octreotide achieved with the administration of LAR at doses 10,20,30 and 60 mg/month. Octreotide blood levels are now commercially available from Inter Science Institute (ISI) (1-800-255-2873).

Theoretically, inadequate circulating levels of octreotide should be associated with poorer clinical symptom control and a higher rate of tumor growth, while blood levels that saturate sst 2 should be associated with better clinical symptom control and better control of tumor growth rates. In the octreotide LAR drug registration trial, LAR doses of 10, 20 and 30 mg per month were associated with mean plasma levels (\pm SD), (n) of 1,153 \pm 748 pg/ml, (n=21), 1,914 \pm 972pg/ml, (n=20) and 4,247 \pm 2,733 pg/ml, (n=24), respectively 1 These levels are in the sub-optimal range for complete

receptor saturation. In this study approximately 40% of patients required the use of “rescue “ medication (subcutaneous aqueous octreotide at doses of 100-500 micrograms three times a day) several days per week. In the study by Woltering et al (submitted for publication) patient plasma octreotide levels were determined and mean plasma levels ranked by the dose of LAR (mg/month). These levels were compared to the data from the Novartis drug registration trial. To completely saturate sst 2 ---plasma levels should be about 10-12,000pg/ml.

Plasma Levels of octreotide by LAR dose (in mg/month)

DOSE	Novartis Study			Inter Science Institute Study		
	MEAN OA (PG/ML)	S.D.	N	MEAN OA (PG/ML)	S.D.	N
10	1,154	748	21	ND	ND	ND
20	1,914	972	20	2,518	1,020	8
30	4,247	2,733	24	5,241	3,004	19
60	ND	ND	ND	10,925	5,330	10

S.D.= Standard Deviation

OA= octreotide acetate

ND= not done

BOLD FACE INDICATES THAT BOTH STUDIES HAD VALUES MEASURED

Subcutaneous octreotide is commonly used for “rescue”, for the control of symptoms during early phases of LAR therapy (while blood levels are increasing) and during specific times like pre, intra and post-operatively to prevent carcinoid crisis. In contrast to the slow rise of blood levels following LAR therapy, after an injection of subcutaneous octreotide blood levels rise rapidly and peak at about 2 hours after an injection. These levels then fall just as rapidly. The half- life of octreotide in the blood is about 90-120 minutes (the half-life is the amount of time that it takes for your body to clear one half of the drug from the blood) After about 6 hours the levels of octreotide have fallen to levels that are not commonly associated with biologic activity. Thus for subcutaneous octreotide to be effective it would need to be given as a subcutaneous shot every 4-6 hours.

Continuous subcutaneous infusions of octreotide acetate have been used by some physicians to take advantage of the rapid absorption of octreotide by the subcutaneous tissues. In this scenario the blood levels of octreotide begin to rise when the pump is turned on and continue to do so until the “steady state” is achieved—usually about 2-4 hours. Likewise, following the cessation of the subcutaneous infusion of octreotide, blood levels begin to fall and are back to insignificant levels after 6-8 hours (depending on dose used).

Thus, the pump is ideal therapy for a patient who needs to be treated with high dose radiolabeled somatostatin analog therapy (like the 177 Lu, 90Y or 111In- based therapies) or has a negative Octreoscan in the past and wants to obtain the maximum sensitivity of this test. Another main advantage of pump- based therapy is the ability of a patient to increase or decrease the rate of infusion on a daily or weekly basis to control symptoms. These changes in rate of infusion produce prompt changes in the blood levels. This type of therapy allows measurement of marker levels on and off (usually allow 12-24 hours for drug to clear from blood stream) therapy -making determination of basal secretion of markers (off therapy) and the efficiency of octreotide to suppress the marker secretion (on therapy with comparison to the off therapy marker value).

Finally, there is a building body of evidence that bolus and steady levels of this drug are handled

differently by the somatostatin receptor-expressing cell.² When a drug is given by bolus injection, the blood levels rise rapidly, and this is associated with progressive binding of the drug to the cell membrane receptor. When the drug levels fall, the drug comes off the receptor and the drug no longer has an effect. Interestingly, in this rapid rise and fall scenario the drug binds and unbinds from the receptor—often compared to a light cord plug and wall socket.

In the case of continuous exposure of the somatostatin subtype 2 (sst 2) receptor to constant levels of octreotide, the receptor no longer acts like a plug and socket—rather the receptor now begins to act like a revolving door (called receptor recycling). In this case the drug binds to the receptor in the cell membrane and the receptor and part of the cell membrane pinch off and go inside the cell (called endocytosis). These endosomes (the part of the cell membrane and the associated sst 2 bound to the octreotide) then begin a process called acidification. When the endosome acidifies the membrane and its receptor opens up; the receptor releases its octreotide inside the cell and the endosome goes back up to the cell surface and reattaches to the membrane (receptor recycling). This keeps happening very quickly, thus allowing more and more octreotide to accumulate within the cell. Once inside the cell the octreotide is either broken down by lysosomes, or alternatively, go to the nucleus of the cell where it appears to control cell division, cell differentiation and a process of programmed cell death called apoptosis. While small amounts of octreotide are internalized when given by bolus injection, the internalization process is enhanced by exposure of the somatostatin receptor (sst 2) to octreotide on a continuous basis. Thus both LAR (after the steady state has been achieved) and the pump-based therapies, at least on a theoretic basis, will have a more profound effect on these cell-growth and differentiation processes than multiple daily doses of octreotide. We have new evidence based on the ability to measure blood levels of octreotide that the bioavailability [the bang for your buck (i.e.) the blood level achieved on a per milligram basis] of subcutaneously administered octreotide may be greater than the LAR form of the medication. When we compared the plasma levels of octreotide in patients receiving octreotide at doses of 60 mg per month (LAR 30 mg every 2 weeks or 2 mg/day by pump) we saw higher blood levels in patients getting their octreotide by pump. This may allow use of less medication on a daily basis in those patients. However economics may play a critical role in the decision to use pump based therapy on a long-term basis. The average wholesale cost (WAC) of the liquid octreotide is significantly greater than the WAC for the LAR form of this medication. The WAC for the 1000mcg/mL 5ml vial (i.e. 5000 mcg or 5mg) is \$977.05 or \$5862 for 30mg. This is equal to \$195 per mg or 19 cents per microgram. In comparison, the WAC for octreotide in the 30 mg LAR dose is \$2466. This is equal to \$82/mg or 8.2 cents per microgram. For the pump to be cost efficient (based on the cost of medication at the wholesale level) the patient would have to use 57% less medication than by the LAR route. In other words, if a patient required 30 mg a month of LAR this would cost (WAC) \$5862. The equivalent number of dollars would buy about 20 mg of octreotide in the aqueous form. Studies are underway to determine the exact comparisons of octreotide blood levels in individuals receiving LAR and pump therapy at equivalent monthly doses (mg/month). These studies will help better define the economic impact of pump-based therapy.

SUMMARY:

In the average patient, the choice of LAR vs. pump-based octreotide therapy is usually controlled by economics. Many insurance companies will not pay for self-administered medication, thus the use of pump-based therapies is limited in those individuals. Those patients whose drug coverage allows either choice may find that they can use less octreotide (mg/month) when given by pump to achieve a given blood level of octreotide than when the same number of milligrams of LAR are given monthly.

In patients who are about to undergo therapy with radiolabeled somatostatin analogs the use of the pump for a three or four-month period prior to this therapy may allow a good quality of life and a maximal efficiency of the radiolabeled material.

In a similar fashion the use of the pump allows the user to turn it off hours (usually 12-24) before measurement of marker level (so that you are actually measuring the baseline of your disease not the efficiency of the octreotide to suppress the marker). Some patients actually have marker measurements on and off pump to determine both the baseline marker secretion of their disease state (off pump measurement) and the efficiency of the octreotide therapy (on pump measurement)

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with comparison to the off pump levels). Likewise the use of the pump allows the patient to turn off the pump 12-24 hours before the administration of an Octreoscan dose to optimize scan accuracy and sensitivity.

In any case, the measurement of plasma octreotide levels in patients with persistent symptoms, continuing need for frequent rescue medication, or continuing tumor growth may allow their physician to adjust their octreotide dose to maximally saturate their sst 2 receptors.

References:

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The reference for the Woltering et al paper cited above will be:

The Effect of Octreotide LAR Dose and Weight on Octreotide Blood Levels in Patients with Neuroendocrine Tumors E.A.Woltering, P.M.Mamikunian, S. Zietz, S.R. Krutzik, V.L.W. Go, A.I. Vinik, E. Vinik, T.M. O'Dorisio, and G. Mamikunian

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