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Potency of Synthroid Tablets

TO THE EDITOR: The article "Maintenance Requirements of L-Thyroxine in the Treatment of Hypothyroidism" by W.A. Kehoe, B.J. Dong and F.S. Greenspan,[1] in the June 1984 issue, contains an addendum which has some incorrect statements that may be misleading to your readers.

The addendum states that Synthroid tablets were reformulated in 1983. In fact, the reformulation took place in 1982. Flint Laboratories' studies show that the bioavailability of the reformulated tablets averages 74%, compared to 70% for the old formulation. The figures of 78% and 100% given in the addendum are actually those reported not for bioavailability but for potency by Stoffer and Szpunar.[2] These potency estimates were, however, based on immunoassay, a technique that has not been validated for measurement of tablet potency. When official USP methodology is used, the potency of Synthroid tablets has not changed with the reformulation.

I hope this will clarify matters for your readers.

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Drs Kehoe, Dong and Greenspan Reply

TO THE EDITOR: We are grateful to Dr Horwitz for formally announcing that their product was reformulated in 1982. We are also pleased to know that it is not the bioavailability that has been changed, although L-thyroxine absorption is very variable.[1-3] However, our clinical experience in 1983-84 of increased biologic potency in patients previously maintained on a stable dose of L-thyroxine is similar to that observed by *Medical Letter* endocrinology consultants[4] and tends to agree with the findings reported by Sawin and co-workers[5] and Stoffer and associates.[6] Sawin and co-workers noted that the actual content of Synthroid tablets prior to reformulation contained 20% to 30% less than their stated content as measured by radioimmunoassay while Synthroid after reformulation contained 100% of the stated amount.[6] Interestingly, both studies were able to correlate the decreased tablet content with decreased response as measured by thyroid function tests.

We do not understand why there should be significant discrepancy in measuring tablet content between high-pressure liquid chromatography (HPLC) and radioimmunoassay but caution that patients previously maintained on a stable dose of L-thyroxine (Synthroid manufactured prior to 1982) may need readjustment of their dose downward to avoid clinical toxicity when receiving the newly reformulated L-thyroxine tablets.

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The Effect of Heparin Dilution on Arterial Blood Gas Analysis

TO THE EDITOR: Drs Dake, Peters and Teague[1] recently published an informative letter about artifacts in arterial blood gas measurements due to dilution with heparin solution. Their information agrees with data published by Dr James Hansen and me,[2] but there are points which I disagree with or wish to clarify.

Adding heparin solution to blood dilutes plasma carbonic acid (H_2CO_3) and, therefore, carbon dioxide; the measured carbon dioxide pressure (Pco_2) then will decrease in proportion to the amount of dilution, as the authors state. I disagree that "when excessive amounts of heparin are added . . . $Paco_2$ [arterial carbon dioxide pressure] is the measurement most profoundly affected," because concentrations of bicarbonate and base excess decrease proportionately with Pco_2. Equal dilution of Pco_2 and bicarbonate accounts for the fact that pH is unaffected, as the authors report. These dilutions change the "metabolic" and "respiratory" components of acid-base measurements proportionately, accounting for clinically unexplained stimultaneous mild primary respiratory alkalosis and primary metabolic acidosis. I agree that pH is also not affected measurably by adding acidic heparin, since the buffering capacity of heparin solution is much less than that of blood.

I disagree on two other points. I think it is incorrect to state that "the partial pressure of a gas in solution is proportional to the solubility coefficient of the gas and the partial pressure of the gas overlying the liquid." The partial pressure of a gas in solution is the same as the partial pressure of the gas overlying the liquid following equilibration. The solubility coefficient could affect partial pressure only indirectly if the gas dissolved significantly, decreasing the amount and partial pressure of the gas overlying the liquid. In the case of CO_2 this would be at most only a miniscule factor.

However, with the high "solubility coefficient" of oxygen in blood, dilution could have a significant effect on measured oxygen pressure (Po_2). We found this effect to be somewhat different from that reported by Dake and co-workers. Unpublished data from our laboratory suggest that the effect of

dilution on Po_2 is predictably very small to very large, depending on partial pressures of oxygen in blood and heparin solution and the dilution. Heparin solution in an unused bottle will normally have a Po_2 of 150 mm of mercury, the same as in air with which it equilibrates. Dilution would therefore raise blood Po_2 if it were originally less than 150 and would lower it if it were greater than 150. Interestingly, we found the absolute pressure of gas in heparin bottles after they have been used was as high as 4 atm (Po_2 approximately 600 mm of mercury) because of the common practice of pumping more air back into the bottle than the volume of solution removed, making the measured blood Po_2 erroneously high. The magnitude of the error depends on the Po_2 of blood and solution and the amount of dilution. If the Po_2 and oxygen saturation of the blood are high and the slope of the oxyhemoglobin dissociation curve is low, "dissolving" oxygen from the gas phase raises Po_2 considerably. An undiluted blood Po_2 of 120 mm of mercury increased to 200 when the blood was diluted 30% by heparin solution with a Po_2 of 400. In contrast, when blood Po_2 and oxygen saturation are low and the slope of the oxyhemoglobin dissociation curve is high, measured Po_2 is affected less. An undiluted blood Po_2 of 50 mm of mercury increased to 58 with the same heparin Po_2 of 400 and 30% dilution. With average pressure in the heparin bottle and average dilution, when blood Po_2 was less than 60, dilution artifacts were small, only rarely exceeding 3 or 4 mm of mercury. When arterial Po_2 was over 100, dilution artifacts were 10 to 15 mm of mercury. Therefore, whatever the initial conditions, the effect of the gas phase and solution Po_2s on measured blood Po_2 would usually not be clinically significant.

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Dr Dake Replies

TO THE EDITOR: We appreciate Dr Simmons' comments which help to clarify and expand points discussed in our prior correspondence.

In stressing the effects of heparin overdilution on the major blood gas measurements of clinical interest directly measured by automated blood gas analyzers (that is, pH, arterial oxygen pressure [Pao_2] and arterial carbon dioxide pressure [$Paco_2$]), we did not address changes in machine calculated values for base excess and bicarbonate.

Indeed, the dilution of arterial blood samples with large amounts of heparin solution will have an effect on base excess and bicarbonate directly proportionate to the decrease in $Paco_2$. Of all the variables examined, however, it is the effect on $Paco_2$ which has the most potential clinical significance.[1-3]

Also, we thank Dr Simmons for sharing data from his laboratory regarding the partial pressure of oxygen in heparin bottles and its effect on the Pao_2 of arterial blood specimens.

Bageant[2] and others have previously described the changes in Po_2 resulting from pumping air into heparin bottles—however, their results and data from our laboratory differ from Dr Simmons' observations in the magnitude of the effect and the potential for clinical importance.

We repeatedly pumped air into different-sized bottles containing heparin solution until a precariously conspicuous bulge was produced in the rubber top. Despite this maneuver designed to produce pressures exceeding those developed during repeated routine clinical use, the maximal heparin solution Po_2 recorded was 244 mm of mercury. In a similar manner, by pushing extra air into a heparin bottle Bageant[2] forced the Po_2 to 275 mm of mercury; however, both these values are far below the Po_2 of "approximately 600 mm of mercury" Simmons found in "heparin bottles after they have been used."

Both Bageant[2] and our laboratory found essentially no difference between the Pao_2 of blood specimens obtained using a minimum of heparin solution equilibrated with ambient pressure and heparin solution from a bottle with positive pressure following repeated air injection.

In summary, despite any differences regarding minor points, there is general agreement that strict adherence to recommended sampling techniques is required to ensure consistently accurate arterial blood gas analysis; this includes utilizing a minimum amount of heparin solution.

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More on Poison Oak Dermatitis

TO THE EDITOR: It is sad to be reminded that some physicians reject new forms of therapy without attempting to determine whether they would allow their patients to be better served. The potential loss to their patients is magnified if the proposed therapy is not only pleasant and safe, but also without significant cost and so effective that it minimizes both the need for prescription medications and the number of visits to physicians' offices. Hot soapless showers in the treatment of poison oak dermatitis[1] seem to be a form of therapy with these advantages.

Their letters[2-4] suggest that Drs Drake, Tromovitch, Stegman, Glogau and Gross have never suggested this technique to any of their patients. I would encourage them to do so before rejecting the treatments as being either inappropriate or useless.

Drs Tromovitch, Stegman and Glogau expressed several concerns including a possible need to specify precise water temperatures. In practice, this precision has not been necessary. None of my patients carry a thermometer into their shower, but rather test the water temperature by hand as they enter in order to assure their safety. Patients have usually found that "comfortably hot" water (obviously warmer than tepid water) gives therapy that is more pleasant than cooler treatments and probably results