SUPPLEMENTARY DATA

Introduction

This appendix provides detailed information justifying the model, additional results, reasoning for the flight recommendations, implications for other pumps and patch pumps and design features of pumps to prevent plunger movement for the paper “Changes in altitude cause unintended insulin delivery from insulin pumps. Mechanisms and implications.”

Justification of model

The model used was an insulin pump with a standard infusion set which was not attached to a person, i.e. the system was “open”.

This model is valid and reflects what would happen when a pump is attached to a human because:

1. Changes in ambient pressure are transferred through the interstitial fluid into the insulin then into the cartridge.
   Water is non compressible and humans consist of 57 to 75% water which transmits changes in ambient pressure through the body. A canula sited in the subcutaneous tissue delivers insulin into the interstitial space. Therefore, the insulin is in direct contact with the interstitial fluid. Changes in ambient pressure results in equal changes in interstitial pressure which is transferred immediately through the insulin in the line and then into the cartridge.

2. The infusion pressure is determined by the infusion rate, interstitial dispensability and interstitial diffusion (these factors are independent of ambient pressure). The interstitial infusion pressure at low infusion rates is less than 5mmHg [1,2].
   The cartridge pressure = ambient pressure + interstitial infusion pressure. Hence, the influence of interstitial infusion pressure on the cartridge pressure is minimal when compared to the ambient pressure.

3. Gas solubility changes linearly as the pressure changes. Hence, the amount of gas that comes out of solution is related to the change in pressure not the absolute pressure values. For example, if the pressure dropped from 760 to 560 mmHg the same amount of gas would come out of solution if the pressure dropped from 780 to 580 mmHg.

Therefore, the results obtained from this model should reflect what is seen in real life. This model has been used by other researchers [3,4].

Reasoning for flight recommendations

1. The cartridge should only contain 1.5mLs of insulin.

The amount of insulin delivered with pressure change depends on the volume of insulin. Hence this will limit the impact if the person does not follow the other recommendations e.g. forgets to disconnect pump off before takeoff.

2. Disconnect the pump before takeoff.

This will prevent excess insulin delivery during ascent in the airplane when the pressure drops.

3. At cruising altitude take the cartridge out of the pump and remove any air bubbles before reconnecting.

When the airplane descends, the air bubbles will be reabsorbed which stops insulin delivery. If the bubbles are removed then the pump will deliver insulin normally during descent because water is non-compressible. Also, the air bubbles can enter the infusion line which prevents insulin delivery.

4. When the airplane has landed, disconnect the pump and prime the line with 2 units. Then reconnect the pump.
If all the air bubbles were not removed before descent then there will be a deficit and the pump will not deliver until it is made up. Disconnecting and bolusing removes any deficit.

5. During flight emergencies, disconnect the insulin pump.

During catastrophic depressurization the decrease in ambient pressure will cause excess insulin delivery because air will come out of solution forming bubbles, bubbles will expand and there is also the potential that the plunger could move.

Implications of this study for other insulin pump brands and patch pumps.
Any insulin pump or patch pump that controls insulin delivery by altering the rate of pushrod movement against a syringe plunger will deliver excess insulin when ambient pressure decreases by:

1. Air coming out of solution and forming bubbles which displace insulin
2. Expansion of existing bubbles

All pumps approved by the FDA have been engineered to prevent plunger movement during “changes in ambient pressure which would reasonably be expected to be encountered according to the intended use of the device” [6]. However, the pumps are usually not tested to the pressure changes that may occur during flight emergencies.

Design features of insulin pumps to prevent plunger movement
Insulin pump companies use four common methods to prevent cartridge plunger movement during pressure change:

1. Venting of the cartridge space to stop the pressure difference occurring.
2. Resistance of the cartridge plunger to movement.
3. Fixation of the cartridge plunger to the push rod (which stops the plunger coming away from the push rod).
4. An alarm that sounds when the plunger separates from the push rod to alert the user.

All insulin pumps and patches currently available utilize at least two of these features to prevent plunger movement with pressure changes. Companies and the FDA have assumed that the pumps will not be exposed to ambient pressures less than 520 mmHg because below this pressure, the oxygen partial pressure is too low for efficient oxygen carriage by hemoglobin and hypoxia occurs.

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Although the pump design features are not enginered to cope with pressure deceases of 500mmHg that may occur during emergency situations, they would limit the amount of insulin delivered and the impact on the individual. Although we saw plunger movement in all the pumps studied, the results may have been different with different conditions or different batches (p-cap venting system for Medtronic and cartridges for Animas).
However, even if the plunger did not move, formation of additional bubbles (from the drop in pressure from 560 to 260 mmHg) would result in an additional 2 units of insulin being delivered from a 3 mL cartridge. Also, any existing bubbles would expand 115% causing additional insulin delivery. Hence, disconnection of the pump during flight emergencies is appropriate.

References

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3. Zisser HC, Bevier W, Dassau E, Jovanovic L. J Diab Sci Tech. 2010; 4(1), 99-103.
4. Aanderud L, Hansen EM: Insulin pumps and drop in pressure. *Tidsskr Nor Laegeforen*. 1994 Feb 20;**114**(5):570-2.
5. Boyle's Law. Available from http://en.wikipedia.org/wiki/Boyle%27s_law Accessed 2 December 2010.
6. Guidance for Industry and FDA Staff - Total Product Life Cycle: Infusion Pump - Premarket Notification [510(k)] Submissions. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm206153.htm Accessed 23 March 2011.

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Supplementary Figure 1. The predicted percentage change in bubble size as ambient pressure decreases from 760 to 380mmHg.
Boyle's Law [5] was used to calculate the percentage increase in bubble size as the ambient pressure decreases. A 200mmHg drop in ambient pressure would cause a bubble to increase in size by 36%.

Boyle's Law