Jadelle – A newly funded long-acting contraceptive implant

From August 1st 2010 Jadelle, a progesterone-only, sub-dermal implant that provides long acting, reversible contraception, has been fully funded in New Zealand. Jadelle (levonorgestrel 2×75mg rods) is licensed for up to five years use. It is dispensed in a pack containing two thin, flexible rods, pre-loaded inside a disposable applicator.

How does Jadelle work?

Jadelle prevents pregnancy by suppressing ovulation, thickening the cervical mucous and altering the endometrial lining to prevent implantation. Suppression of ovulation varies on an individual basis and wanes over successive years.

Levonorgestrel is rapidly released from the rods after insertion, in sufficient quantity to provide contraception within 24 hours. Additional barrier contraception may be required depending on the stage of the woman's menstrual cycle at insertion and the previous contraceptive method used.[1] (Refer to the Medsafe data sheet for more information on how to start Jadelle).

Insertion and removal

A minor surgical procedure is required to insert the rods just beneath the skin of the inner, upper arm (usually the non-dominant side) in a narrow, V-shaped pattern. Removal of the rods also requires minor surgery which is usually straightforward, however in some cases removal may take longer than insertion and be more painful.[2] It is recommended that insertion and removal are performed by a trained provider and that enough procedures are undertaken to maintain skills.[1] Some GPs may prefer to refer their patients to Family Planning clinics for insertion and removal.

Return to fertility after removal

Implants may be removed at any stage of the menstrual cycle. Rods may stay in place for up to five years after insertion. They can be removed sooner for personal or medical reasons. Once the implants are removed there is an almost immediate loss of contraceptive effect.[1]

Continuation of treatment with Jadelle implants

A patient who chooses to continue using Jadelle implants for contraception may have a new set of rods inserted on the same day as the old set is removed. The new rods may be inserted through the same incision used for removal and the rods placed in the same or opposite direction as the previous set.[2]

Efficacy of Jadelle

Jadelle has an average pregnancy rate over a five year period for all women of less than 1%.[2] Clinical trials have shown that although the efficacy of Jadelle is highest in the first four years of use, contraceptive effectiveness is still acceptable in the fifth year of use. Removal or replacement of the rods is advised after the fifth year as effectiveness decreases.[2]

Medsafe recommends that removal or replacement is considered after four years of use, in women who weigh more than 60kg.[1] This is because the serum concentration of levonorgestrel decreases with increased weight, which may reduce levonorgestrel to a less effective level towards the end of the five-year life of the implant. Individual response to levonorgestrel varies and serum concentration alone is not predictive of the risk of pregnancy, but this small decrease in efficacy may be an important consideration for some patients. The annual pregnancy rate in the fifth year of use per 100 women

is 1.1 in those weighing more than 60 kg and 0.5–0.9 in those weighing less than 60 kg.

Menstrual irregularities are frequently reported

Because Jadelle contains no oestrogen, disruption of the menstrual cycle is the predominant adverse effect. The majority of women who use Jadelle will experience bleeding irregularities, which may include prolonged bleeding or spotting, heavy bleeding, spotting between periods, no bleeding at all or any combination of these patterns.[2] Irregularities in bleeding do not alter the pregnancy rate.

Approximately 14% of women who use Jadelle discontinue it before five years due to menstrual irregularities.[2] There is no way of predicting what kind of menstrual change a woman will have with Jadelle therefore adequate counselling prior to insertion is essential and likely to enhance patient acceptability of the method.

Other adverse reactions, reported in clinical trials by more than 10% of women, included local reactions at the insertion site e.g. pain, skin irritation or discolouration and symptoms similar to those experienced with any hormonal contraceptive such as dizziness, headache, nausea, breast or pelvic pain, vaginal discharge and weight gain.[1,2]

Interactions

Medicines that induce hepatic enzymes such as phenytoin and carbamazepine may impair the contraceptive action of Jadelle, therefore an alternative method of contraception is recommended in women who take such medicines on a long-term basis. If medicines that induce hepatic enzymes are required short-term, an additional non-hormonal form of contraception should be used during and for four weeks after treatment with the enzyme-inducing medicine.[1]

Contraindications

Contraindications to the use of Jadelle include:[1]

- Allergy to levonorgestrel or to any of the ingredients listed in Jadelle implants
- Undiagnosed vaginal bleeding
- Pregnancy
- Active thrombosis
- Presence of, or history of, severe liver disease if liver function tests remain abnormal
- Presence of, or history of, benign or malignant liver tumours
- Suspected or active breast or endometrial cancer

References:

1. Bayer New Zealand Limited. Jadelle. Medsafe Medicine Safety Data Sheet. Available from www.medsafe.govt.nz (Accessed Sept, 2010).
2. Sivin I, Nash H, Waldman S. Jadelle levonorgestrel rod implants: A summary of scientific data and lessons learned from programmatic experience. Population Council: New York; 2002. Available from: www.popcouncil.org/pdfs/jadelle_monograph.pdf (Accessed Sept, 2010).

Obesity and sibutramine: a risky combination

Sibutramine (Reductil®) has now been withdrawn from the New Zealand market, after many years of safety concerns.

The main concern with sibutramine use is the increased risk of adverse cardiovascular and cerebrovascular events. As concerns grew, so did restrictions, from stronger warnings to complete withdrawal from use.

Achieving the safe use of sibutramine illustrates the difficulty in balancing research and trial results with the "real world" clinical setting. Theoretically sibutramine can be beneficial in aiding weight loss and therefore reducing risk factors for cardiovascular disease. Contraindications to the use of sibutramine include a history of coronary artery disease, e.g. angina, myocardial infarction, congestive heart failure, a history of cerebrovascular disease, inadequately controlled hypertension and people aged over 65 years.[1]

However in the "real world", it is not as straight forward as the condition that sibutramine is indicated for, i.e. being overweight or obese, is itself a major risk factor for cardiovascular disease. Hence all patients being considered for sibutramine will have an elevated risk of cardiovascular disease, likely resulting in an increase in the risk of adverse effects with sibutramine. It is very difficult to predict which patients will suffer an adverse cardiovascular or cerebrovascular event when treated with sibutramine. This is essentially the reason why Medsafe has made the decision to withdraw the product.

Patients are now faced with the prospect of switching to another medicine to aid weight loss or managing their weight by diet and lifestyle alone.

For further information about weight loss medications, see: "Medicines for weight loss - do they work?" BPJ 27 (April, 2010)

Quantifying the risk of sibutramine

Post-marketing "real-life" use of sibutramine in a general population has been undertaken in New Zealand as part of the Intensive Medicines Monitoring Programme (IMMP). Case reports from the study cohort (15 686 voluntary reports) identified a total of 1322 adverse events; of these 191 (14%) were assessed as cardiovascular events including new onset hypertension, palpitations, hypotensive events and tachycardia. Of these adverse cardiovascular events, four resulted in death of the patient, including myocardial infarction and stroke.[2]

Further assessment of the four deaths in the IMMP study identified that some patients had conditions, e.g. pre-existing hypertension, that should perhaps have contraindicated the use of sibutramine.[2]

The Sibutramine Cardiovascular OUTcomes (SCOUT) study was a randomised, double-blind, placebo-controlled study involving approximately 10 000 obese and overweight patients, with cardiovascular disease and/or type 2 diabetes, treated over a six year period. Patients treated with sibutramine had a 16% increased risk of non-fatal cardiovascular events compared with those taking a placebo.[3] The overall risk of death was 1.2 per 100 years of sibutramine exposure, which is approximately 10-fold higher than the estimated rate of death reported in the IMMP study.[2] However, it is difficult to make a meaningful comparison between an observational study based on IMMP reports and a randomised controlled trial.

Most of the patients enrolled in the SCOUT study had contraindications for sibutramine. However this may represent normal clinical use in the "real world" setting because it is not always possible to identify underlying cardiovascular disease in patients who are obese or overweight.[4]

An important difference between the study population in SCOUT and the IMMP cohort was patient age. The median age of subjects in SCOUT was 63 years compared with 43 years in the IMMP study cohort. As age is one of the most important independent risk factors for cardiovascular disease, the 20-year difference between the two study populations may be one of the reasons for the higher rate of death observed in the SCOUT study.[2]

"Take-home" messages

- Contraindications do not always prevent use of a medicine in "real life"
- Cardiovascular risk may not always be apparent or easily assessed, especially in overweight and obese patients
- Patient safety comes first. The IMMP cohort results do not necessarily show a significant safety issue with sibutramine, when used in patients without contraindications, but the unpredictability of cardiovascular risk assessment and difficulty in ensuring safe prescribing means that withdrawal from the market is a sensible safety measure.

For further information about the Medsafe decision, see: "Withdrawal of sibutramine (Reductil) in New Zealand". Ministry of Health, Media Release, 11 October 2010. Available from: www.moh.govt.nz

References

1. Abbott Laboratories (NZ) Ltd. Reductil datasheet, Version 12, 2010. Available from: www.medsafe.govt.nz (Accessed Oct, 2010).
2. Harrison-Woolrych M, Ashton J, Herbison P. Fatal and non-fatal cardiovascular events in a general population prescribed sibutramine in New Zealand. Drug Safety 2010;33(7):605-13.
3. James WPT, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 2010; 2(363):905.
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