CLINICAL STUDY

GLP-1 analogues as a new treatment option for hypothalamic obesity in adults: report of nine cases

Flavius Zoicas, Michael Droste\textsuperscript{1}, Bernhard Mayr, Michael Buchfelder\textsuperscript{2} and Christof Schöfl

Division of Endocrinology and Diabetes, Department of Medicine 1, Friedrich-Alexander-University Erlangen-Nuremberg, Ulmenweg 18, 91054 Erlangen, Germany, \textsuperscript{1}Endocrine Practice, Oldenburg, Germany and \textsuperscript{2}Department of Neurosurgery, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany

(Correspondence should be addressed to C Schofl; Email: christof.schoefl@uk-erlangen.de)

Abstract

Background: Patients with hypothalamic pathology often develop morbid obesity, causing severe metabolic alterations resulting in increased morbidity and mortality. Glucagon-like peptide-1 (GLP-1) analogues improve glycaemic control in type 2 diabetic patients and cause weight loss in obese patients by yet unknown mechanisms. Here we tested whether GLP-1 analogues were also effective in the treatment of obesity and associated metabolic alterations in patients with hypothalamic disease.

Methods: Nine patients (eight with type 2 diabetes mellitus) with moderate to severe hypothalamic obesity were treated with GLP-1 analogues for up to 51 months. Body weight, homeostasis model assessment - insulin resistance (HOMA-IR), HbA1c and lipids were assessed.

Results: Eight patients experienced substantial weight loss (13.1 ± 5.1 kg (range 9 to 22)). Insulin resistance (HOMA-IR = 3.2 ± 3.5 (range -9.1 to 0.8)) and HbA1c values (1.3 ± 1.4% (range -4.5 to 0.0)) improved under treatment (24.3 ± 18.9 months (range 6 to 51)). Five patients reported increased satiation in response to the treatment. Two of the eight patients complained about nausea and vomiting and one of them abandoned therapy because of sustained gastrointestinal discomfort after 6 months. One patient suffered from intolerable nausea and vomiting and discontinued treatment within 2 weeks.

Conclusion: GLP-1 analogues can cause substantial and sustained weight loss in obese patients with hypothalamic disease. This offers a new approach for medical treatment of moderate to severe hypothalamic obesity and associated metabolic alterations.

European Journal of Endocrinology 168 699–706

Introduction

Patients with brain tumours such as craniopharyngiomas, which involve the hypothalamic region, are at high risk for the development of obesity (1, 2, 3, 4, 5, 6, 7, 8). Hypothalamic obesity appears to result from tumour- or treatment-related damage of hypothalamic nuclei especially in the ventromedial region that causes impairment of mechanisms controlling satiety, hunger and energy expenditure (9, 10, 11, 12). At presentation, about 15% of adult patients suffering from a craniopharyngioma complain about excessive weight gain or are obese (1, 2, 7, 13). During long-term follow-up, excessive weight gain has been reported in up to 67% of craniopharyngioma patients after surgery with or without adjuvant radiotherapy (1, 2, 3, 4, 7, 14). Hypothalamic obesity is often associated with disastrous metabolic and psychological consequences leading to severe morbidity, impaired quality of life and reduced life expectancy (2, 7). Features of the metabolic syndrome such as abdominal obesity, dyslipidaemia, hyperinsulinaemia caused by insulin resistance and elevated blood pressure are commonly seen in these patients (2, 3, 7, 15, 16), which contribute to the increased risk for cardiovascular morbidity and long-term mortality (2, 7, 16, 17, 18).

Thus, the necessity for treatment is vital but treatment of hypothalamic obesity is difficult and often intractable. In the affected patients, weight gain is mostly unresponsive to diet and exercise interventions. Targeted pharmacological treatment is limited and consists of suppression of insulin secretion with octreotide and/or sympathomimetics (19, 20, 21, 22). Methylphenidate, a dopamine reuptake inhibitor, has been shown to reduce energy intake and especially the intake of fat (23). Furthermore, in animal studies, methylphenidate increased locomotor activity (24, 25) and thus might be a helpful compound to overcome physical hypoactivity, which is common in patients with hypothalamic obesity (10, 19, 26). Orlistat, a gastrointestinal lipase inhibitor, has limited efficacy and can be associated with intolerable side effects that can preclude its use (27, 28). Several other drugs have recently been withdrawn from the market due to severe
side effects, e.g. sibutramine, which was associated with a high risk of cardiovascular events (29). Therefore, bariatric surgery remains the only option for the treatment of morbid hypothalamic obesity (30, 31). Depending on the surgical intervention, however, patients require life-long surveillance and nutritional supplementation (30). Thus, there is a clear need for novel therapeutic options, which are both effective and well tolerated with an acceptable long-term safety profile.

Analogues of glucagon-like peptide-1 (GLP-1), which is a gut-derived incretin hormone, are used for the treatment of type 2 diabetes mellitus. They stimulate glucose-dependent insulin release and inhibit glucagon secretion, thereby improving glycemic control (32). In addition, treatment with GLP-1 analogues promotes weight reduction are yet to be unravelled, there may be a combination of effects on the gastrointestinal tract as well as on the brain (37, 38, 39, 40). Although the precise mechanisms that mediate the effects of GLP-1 analogues on weight reduction are yet to be unravelled, there may be a combination of effects on the gastrointestinal tract as well as on the brain (37, 38, 39, 40). It is unknown whether GLP-1 analogues can lead to weight loss in patients with obesity caused by hypothalamic damage, and whether these compounds could be an option for their treatment. We therefore treated nine patients with moderate to severe hypothalamic obesity with a GLP-1 analogue and assessed changes in weight and metabolic parameters such as insulin resistance, HbA1c and lipid metabolism.

### Materials and methods

Nine patients with tumours involving the hypothalamic region and obesity were treated either with the GLP-1 analogue exenatide (eight) or with liraglutide (one). Six patients had a craniopharyngioma, one a pilocytic astrocytoma, a germinoma and a hypothalamic hamartoma respectively. Eight patients had at least one operation, and one of them received adjunctive radiotherapy. The patient with a germinoma was irradiated only. All patients suffered from partial (n = 2) or panhypopituitarism (n = 7) with or without central diabetes insipidus and received hormone replacement therapy (Table 1), which had been optimized prior to GLP-1 analogue therapy (Table 1), which had been optimized prior to GLP-1 analogue therapy. Eight patients suffered from type 2 diabetes mellitus. The patients were examined regularly and body weight and blood pressure were recorded. Blood glucose, HbA1c, total cholesterol, HDL- and LDL-cholesterol, and triglycerides were measured by routine laboratory methods from fasting blood samples. Insulin was determined by a chemiluminescence immunoassay (Immulite 2000; Siemens, Eschborn, Germany). Insulin sensitivity was quantified by calculating HOMA-IR.

### Table 1 Effect of GLP-1 analogue treatment on body weight and metabolic parameters in eight patients with hypothalamic obesity.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treat</th>
<th>Base</th>
<th>Base</th>
<th>Treat</th>
<th>Base</th>
<th>Base</th>
<th>Treat</th>
<th>Treat</th>
<th>Base</th>
<th>Total group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>153</td>
<td>186</td>
<td>160</td>
<td>153</td>
<td>186</td>
<td>160</td>
<td>153</td>
<td>186</td>
<td>160</td>
<td>153±18.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9</td>
<td>29.4</td>
<td>26.1</td>
<td>25.9</td>
<td>29.4</td>
<td>26.1</td>
<td>25.9</td>
<td>29.4</td>
<td>26.1</td>
<td>25.9±4.2</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.3</td>
<td>5.3</td>
<td>6.3</td>
<td>6.3</td>
<td>5.3</td>
<td>6.3</td>
<td>6.3</td>
<td>5.3</td>
<td>6.3</td>
<td>6.3±0.7</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>260</td>
<td>158</td>
<td>213</td>
<td>260</td>
<td>158</td>
<td>213</td>
<td>260</td>
<td>158</td>
<td>213</td>
<td>219±42</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>114</td>
<td>84</td>
<td>129</td>
<td>114</td>
<td>84</td>
<td>129</td>
<td>114</td>
<td>84</td>
<td>129</td>
<td>129±33</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6±0.7</td>
</tr>
<tr>
<td>Hormone replacement therapy (daily doses)</td>
<td>0.05 mg</td>
<td>3.7 mg</td>
<td>0.15 mg</td>
<td>0.1 mg</td>
<td>0.2 mg</td>
<td>0.15 mg</td>
<td>0.05 mg</td>
<td>0.1 mg</td>
<td>0.2 mg</td>
<td>0.15 mg</td>
</tr>
</tbody>
</table>

*P < 0.05; †P < 0.01 vs baseline.

Values were obtained while the patient was on lipid-lowering medication.

Downloaded from Bioscientifica.com at 02/14/2019 01:35:15PM via free access
using fasting glucose and insulin values and the HOMA2 program which was kindly provided by Dr Levy (41, 42).

Values are means ± s.d. Statistical analysis was performed using SigmaPlot version 11 (Systat Software, Erkrath, Germany). Pre- and post-treatment data were compared by the Wilcoxon signed-rank test for paired comparisons. Significance was considered at $P < 0.05$.

Case reports and results

Patient 1

A 49-year-old Caucasian man complained about 30 kg of weight gain within 6 months, intermittent headaches, insomnia, lethargy, polydipsia, nocturia and impairment of vision. Type 2 diabetes mellitus was diagnosed and further investigations revealed a cystic tumour arising in the sellar region and extending to the hypothalamus on a cranial magnetic resonance imaging (MRI). The patient was operated twice in April 2007 and August 2007 via a transcranial route with complete tumour removal of an adamantinomatous craniopharyngioma. Post-surgery, the patient suffered from persistent panhypopituitarism and diabetes insipidus. Despite adequate hormonal replacement therapy (Table 1), good glycaemic control under metformin therapy (1000 mg BID) and repeated dietary and lifestyle counselling, no weight loss could be achieved (Fig. 1). In January 2010, treatment with exenatide (5 µg s.c. once daily) was started. The patient reported a feeling of satiety with significantly reduced meal sizes. He lost a maximum of 34 kg of weight within 8 months of therapy (Fig. 1). Dyslipidaemia, insulin resistance and HbA1c improved (Fig. 2A, B and C) as well as subjective quality of life. No adverse events of exenatide were reported. Exenatide was paused for 6 months. Remarkably, his body weight and metabolic parameters remained fairly stable during this period. As reported by the patient, his physical fitness had substantially improved in response to weight loss, so that he could exercise on a regular basis. Thus, it appears that maintenance of body weight was primarily achieved by lifestyle changes rather than by a delayed action of exenatide. Thereafter, exenatide (5 µg s.c. once daily) was restarted and in October 2011, the dose was increased to 5 µg twice daily because of a moderate weight gain. Under this therapy, body weight stabilized. HbA1c was 5.3%, triglycerides further improved, but a slight increase in insulin resistance and cholesterol levels were observed (Table 1 and Fig. 1).

Patient 2

Patient 2 was a 46-year-old Caucasian man who suffered from a pilocytic astrocytoma (WHO I) within the third ventricle. The tumour was excised in 2002 and a ventriculoperitoneal shunt was installed. In 2006, a cranial MRI showed two new lesions, one in the suprachiasmatic region close to the third ventricle (18×10×17 mm) and a second one in the left thalamus (9×8 mm). A fronto-temporal trepanation was performed and both tumours were completely removed. Post-surgery, the patient developed partial hypopituitarism with GH deficiency and hypogonadism (treatment, see Table 1). Furthermore, the patient experienced a continuous and considerable weight gain, reaching a maximum BMI of 44.7 kg/m², and developed dyslipidaemia, type 2 diabetes mellitus, arterial hypertension and obstructive sleep apnoea syndrome. The patient was put on metformin (2000 mg/day) and in July 2008, treatment with exenatide (5 µg s.c. twice daily) was initiated and further uptitrated to 10 µg BID. Within the first 2 years of treatment, the patient lost 20 kg of body weight, which remained relatively stable after that. Glycaemic control improved over time, but dyslipidaemia remained unchanged (Table 1). The patient reported a normal appetite and a sensation of satiety, which he did not have prior to exenatide treatment. No adverse events were reported.

Patient 3

A 17-year-old man, who suffered from drug-resistant epilepsy, underwent a partial left-sided temporal lobectomy in September 2006, and in October 2008, a hypothalamic hamartoma (10×6 mm) in the lower left-side part of the third ventricle was excised and a callosotomy was performed. After the second operation, the patient complained about a weight gain of 40 kg in 6 months (maximum BMI 39.2 kg/m²),

![Figure 1 Changes in body weight in response to exenatide therapy in case 1.](https://www.eje-online.org)
a loss of sensation of thirst and satiety, and a general hypodynamia. Partial hypopituitarism was diagnosed with alterations in the somatotrope, gonadotrope and thyrotrope axis (treatment, see Table 1). Furthermore, moderate hypertriglyceridaemia developed. The patient was put on metformin (850 mg BID) and methylphenidate (10 mg once daily) in order to counteract weight gain and hypoactivity. This treatment approach, however, was not tolerated because of gastrointestinal side effects and several grand mal seizures, which developed under this treatment. Therefore, off-label treatment with exenatide (5 μg BID) was started. Within 6 months of treatment, the patient lost 9 kg of body weight. Concerning insulin resistance and dyslipidaemia, however, no improvement was noticed (Table 1).

**Patient 4**

A 35-year-old man experienced headaches, psychotic changes and polydipsia. A suprasellar craniopharyngioma extending to the hypothalamus (20 × 30 mm) was diagnosed and a transfrontal operation was performed in 1997. Post-surgery, the patient suffered from panhypopituitarism and diabetes insipidus (treatment, see Table 1). The patient experienced continuous weight gain and in 2001, type 2 diabetes mellitus was diagnosed. Despite metformin (850 mg TID), the patient put on further weight, reaching a BMI of 30 kg/m², and glycaemic control was unsatisfactory (HbA1c 9.5%). In April 2008, therapy with exenatide (5 μg BID) was initiated. Upon treatment, the patient reported for the first time a sufficient sensation of satiety since the operation in 1997. Despite nausea and intermittent vomiting, he insisted on continuing therapy because of an overall subjective improvement of quality of life. Over 44 months of treatment, the patient lost 9 kg of weight (BMI 27.5 kg/m²), and glycaemic control and dyslipidaemia improved (Table 1).

**Patient 5**

Patient 5 is a Caucasian man born in 1974 who presented with polyuria and polydipsia at the age of 22 years. A suprasellar germinoma was diagnosed and the patient received radiation therapy. Post-irradiation, he developed panhypopituitarism, which was treated as depicted in Table 1. In 2002, type 2 diabetes mellitus was diagnosed and treated with metformin (3 × 850 mg daily). Because of insufficient glycaemic control (HbA1c 8.4%), the patient was switched to exenatide (5 μg s.c. BID) in September 2007. At that time, his BMI was 27.2 kg/m². After 51 months of treatment, the patient had lost 13 kg and reached normal weight (BMI 23.2 kg/m²), and his HbA1c as well as dyslipidaemia had improved (Table 1). Initially, the patient reported nausea but no vomiting, which subsided with time.
Patient 6

Patient 6 was born in 1959. At the age of 47 years, he developed headaches and visual impairment. A large suprasellar craniopharyngioma was diagnosed and the tumour was operated via a transcranial route. Post-operatively he developed panhypopituitarism and central diabetes insipidus, which was treated as given in Table 1. The patient gained 10 kg of body weight and in 2006, type 2 diabetes mellitus was diagnosed. Metformin therapy (2×1000 mg) was initiated but glycaemic control was moderate (HbA1c 7.3%) and obesity (BMI 33.9 kg/m²) persisted. Exenatide treatment with 5 µg s.c. BID was started in September 2009. After the first week of therapy, the patient reported that his binge-eating disorder had vanished. However, because of uncontrolled vomiting even with the lowest dose of 5 µg exenatide once per day, the treatment was stopped after 6 months. Within this short period of therapy, the patient lost 9 kg of body weight, and glycaemic control and hypertriglyceridaemia improved (Table 1).

Patient 7

A Caucasian man born in 1947 complained about headaches and deterioration of vision in 1972. A craniopharyngioma was diagnosed and the tumour was operated. Because of several relapses, multiple surgeries followed and in 1989, the patient received radiation therapy. He developed complete pituitary deficiency and diabetes insipidus as a consequence of therapy (treatment, see Table 1). Over the years, the patient became grossly obese (BMI 47.1 kg/m²) and in 1995, type 2 diabetes mellitus was diagnosed. Despite rigorous dietary measures and various antidiabetic drug regimens including metformin in combination with glimepiride and rosiglitazone and, later on, intensified insulin therapy, glycaemic control was unsatisfactory (HbA1c 7.9%). Therefore, in July 2008, exenatide treatment was started (5 µg s.c. once daily). Because of intolerable nausea and vomiting, the treatment was abandoned after 2 weeks. The patient underwent bariatric surgery (gastric banding). At the last visit, BMI was 40 kg/m² and under metformin monotherapy (850 mg BID), HbA1c was 5.3%.

Patient 8

A 38-year-old man presented with 20 kg weight gain within several months and was diagnosed with a papillary craniopharyngioma in 2006. The tumour was operated via a transcranial route. Post-surgery, the patient suffered from panhypopituitarism and diabetes insipidus, for which he was treated (Table 1). Post-operatively, his body weight further increased by 13 kg and in 2008, type 2 diabetes mellitus was diagnosed, which was treated with metformin (850 mg BID). In May 2010, exenatide was started (5 µg BID). The patient reported an increased sensation of satiety and after 12 months of therapy, the patient had lost 9 kg of body weight. HbA1c remained unchanged, while insulin resistance and triglyceride levels improved (Table 1).

Patient 9

Patient 9 was born in 1971 and was diagnosed with an adamantinomatous craniopharyngioma in 2008, which was transcranially excised. After surgery, the patient developed complete pituitary deficiency, diabetes insipidus, severe obesity and type 2 diabetes mellitus, which were treated as depicted in Table 1. Because of poor glycaemic control (HbA1c 10.4%) and a BMI of 41.8 kg/m², treatment with liraglutide (0.6 mg/day) was commenced in October 2010. The patient reported less hunger and an increased feeling of satiety. After 8 months of therapy, the patient showed significant weight loss, reaching a BMI of 35.3 kg/m², had improved glycaemic control and insulin resistance, as well as decreased cholesterol levels (Table 1).

In this series of nine patients with obesity caused or aggravated by hypothalamic pathology and/or its therapy, treatment with GLP-1 analogues was relatively well tolerated. Five patients reported increased satiation after meals, which they had not experienced prior to the treatment. Three patients reported nausea and vomiting, of whom one patient stopped therapy after 2 weeks and another one after 6 months. In the third patient, symptoms subsided and therapy was continued. In the eight patients who received treatment for at least 6 months (24.3±18.9 months, range 6–51), the average weight loss amounted to 13.1±5.1 kg (range 9–22; P<0.01) and BMI decreased from 37.6±7.2 to 33.4±6.3 kg/m² (P<0.01). The average daily dosages were 11.4±3.8 µg for exenatide and 0.6 mg for liraglutide. HbA1c improved by 1.3±1.4% (P<0.05, range 0–4.5) and insulin sensitivity improved as indicated by HOMA-IR, which decreased from 6.9±4.9 to 3.7±1.6 (P<0.05). With the exception of triglycerides, which dropped from 430±180 to 324±162 mg/dl (P<0.05), no improvement in lipid parameters (total, HDL- or LDL-cholesterol) was observed.

Discussion

Body weight control is complex involving several brain regions, orexigenic and anorexigenic pathways, as well as central and peripheral signalling molecules that regulate food intake as well as energy consumption and locomotor activity (43, 44, 45). Within this complex interplay, the hypothalamus is considered as one of the key structures for processing and integration of central and peripheral pathways and signals. Consistently, patients with tumours involving the hypothalamus are often hypoactive and complain about increased food

www.eje-online.org
intake and a loss of satiety sensation (2, 7, 9, 10, 11). Consequently, they develop severe obesity and obesity-associated morbidities such as dyslipidaemia, diabetes mellitus and cardiovascular disease (1, 2, 3, 7). Both structural and functional disruptions of regulatory pathways may explain why attempts to reduce and control body weight by employing behavioural interventions or drug treatments fail in most patients. Even with bariatric surgery, which often remains the only option in morbidly obese patients, sustained weight loss may not be achieved and outcome data are conflicting (4, 30, 31, 46).

In this case series, treatment with GLP-1 analogues promoted substantial weight loss in eight of the nine patients with hypothalamic obesity. This could be sustained for as long as 51 months, which was the longest observation period in this series. Weight loss was associated with a favourable metabolic and cardiovascular risk profile as insulin resistance, glycaemic control and hypertriglyceridaemia significantly improved under treatment. Cholesterol levels, however, did not change, which is consistent with the results from some but not all randomized trials reporting about the effects of GLP-1 analogue treatment on lipids (34, 36). The effects on body weight and metabolic parameters were at least as pronounced as previously reported from obese diabetic and non-diabetic patients without hypothalamic pathology (33, 34, 35, 36). Interestingly, the average daily drug doses required were relatively low and in one patient even below the recommended minimal daily dose (47). Thus, it appears that some patients with hypothalamic obesity are rather sensitive to GLP analogue therapy. Fortunately, it seems that this does not necessarily apply to the most common adverse effects of this therapy, namely nausea and vomiting. This is of interest as in patients with type 2 diabetes, an association between increased nausea and weight loss has been suggested (48). Our observation, however, is consistent with studies from animal models that show that GLP-1-dependent actions on food intake and visceral illness can be dissociated (40, 49) and are confined to distinct brain areas (40).

The mechanism whereby exogenous GLP-1 or its analogues trigger weight loss is only incompletely understood. As GLP-1 receptors are expressed in the brain as well as in peripheral tissues, weight loss might be caused by a combination of central and peripheral GLP-1 actions (37, 38, 40, 50). In the brain, GLP-1 acts to increase energy expenditure and to reduce food intake according to animal studies (38, 40). With respect to the inhibition of food intake, this involves GLP-1 receptor activation in the paraventricular nucleus of the hypothalamus, the hindbrain and in the nuclei of the mesolimbic reward system (37, 38, 40, 51). In addition, there is good experimental evidence that peripheral GLP-1 via activation of peripheral GLP-1 receptors and through the activation of afferent vagal neurotransmission from the intestine could reduce meal sizes and increase satiation (37, 38, 40). Clinical data from human studies suggest that weight loss in patients treated with GLP-1 or its analogues is predominantly caused by decreased food intake rather than through changes in energy expenditure (40). This may involve delayed gastric emptying and increased satiation caused by peripheral and central actions of exogenous GLP-1 (38, 40, 52).

It can be assumed that in our patients, damages to the structure and function of hypothalamic nuclei were quite heterogeneous as the underlying pathologies differed in size, local extension and treatment. Despite this, all eight patients who tolerated the treatment lost weight, which indicates either that none of our patients had damaged hypothalamic structures relevant for GLP-1 analogue-induced weight loss or that mechanisms were involved that do not require intact hypothalamic functioning. Whatever the mechanisms are, our series clearly demonstrates that GLP-1 analogues are capable of inducing weight loss in patients with obesity caused or aggravated by hypothalamic damage. Although this is not a controlled study and the number of treated patients was relatively small, treatment with GLP-1 analogues holds promise as a novel therapeutic option to reduce or control body weight and to improve metabolic co-morbidities in these patients. It remains to be shown which patients with hypothalamic obesity profit most from GLP analogue therapy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work is part of the Neurotrition Project, which is supported by the FAU Emerging Fields Initiative.

References


51 Alhadeff AL, Rupprecht LE & Hayes MR. GLP-1 neurons in the nucleus of the solitary tract project directly to the ventral tegmental area and nucleus accumbens to control for food intake. *Endocrinology* 2012 153 647–658. (doi:10.1210/en.2011-1443)


Received 13 November 2012
Revised version received 21 December 2012
Accepted 7 February 2013